EXHIBIT 1
DATE 3/18/13
SB 296

February 22, 2013

Brenna Faulk
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Victor, MT 59875
406-961-6890

Hello,
My name is Brenna Faulk, I have neuroborrelliosis, (late stage Lyme disease, or chronic Lyme Disease. It appalling that American citizens who are bedridden are all but ignored by our government and medical professionals. Even the physicians that understand the disease have to practice 'underground' so to speak to protect their patients and themselves. There is a huge controversy over what type of treatment is required to heal a Lyme patient. Bottom line is that treatment is going to be different for each individual, but the IDSA and CDC are using reporting guidelines for diagnostic and treatment guidelines. That is NOT what they were developed for. The insurance companies are all too willing to comply, since it enables them not to pay for many claims. Meanwhile patients are going broke trying to get better, some commit suicide because they cannot take the years upon years of pain and not to mention the isolation. They cannot work because they are too sick, but get denied disability because according to guidelines they should have been 'healed' after a month of antibiotics. But all to often diagnosis comes after the bacteria have had over a year or two to spread and become elusive to treatment. There are so many, issues to address before this silent epidemic will be brought under control. Physicians MUST tell patients the unreliability of CDC testing standards and give them the choice to use a more specific lab (Igenex is specific to vector born illnesses)

1. Physician MUST be aware that this illness knows no borders. It can be n ANY state! (I was told at the Mayo Clinic there is no Lyme in Montana, and they recommended therapy, a year later I could barely walk).
2. Physicians Must be protected from action for treating the patient in whatever way the physician and patient feel is best after disclosing ALL available options.
3. More public awareness should be done. Educating the public as too risk factors, and signs and symptoms to look out for.
4. People need to be educated on the multiple ways lyme can be transmitted.

Since I am stuck in bed 80% of the time to manage the pain, I read so many stories of the injustices being done. We Lymies NEED help from the national media. May is Lyme Disease Awareness month. I am organizing a National Flash Mob to raise awareness for us in a fun positive way. It will take place May 4th round noon. I have twenty-two states signed on so far for a public Flash Mob and still growing. Please help us promote awareness and stand up against the odds for this debilitating disease.

Brenna Faulk

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RAVALLI REPUBLIC

Lyme disease: Doctors don't always know

3 HOURS AGO

Is there Lyme disease in Montana? Yes. Do our doctors want to acknowledge it? No.

My daughter has had the symptoms for many years and no one has been able to figure it out. Her attending physician put her on a month's worth of antibiotics and many other prescriptions and was told that would make her better.

After taking the antibiotics for 28 days, she developed Bell's Palsy. She was again given antibiotics and steroids, and again, this was going to fix everything. After her physician saw the final test results, she was told to go see an infectious disease doctor for answers. While she waits for doctors to decide what is wrong with her, she converses with a friend of hers, whose son went through the same thing with the doctors around here. He was diagnosed with Lyme, too, and the only help they got was through a doctor in Bozeman. So my daughter sent her stuff there and within one day was called and told that she had Lyme disease. The doctor wanted to see my daughter as soon as she could.

We finally have answers and treatment with a regimen that will help her – instead of being told "I am not sure what it is and hope I don't see you again."

While with this doctor we found out that my daughter is not the only case that she is treating in our area so far this year; we found that very interesting.

There are probably people out there right now who have no idea what is wrong with them, and our local doctors don't either, and these people could be struggling with Lyme. There is a great documentary to watch called "Under Our Skin."

If you have been diagnosed with Lyme, hope is out there. Don't give up.

Mary Ann Haskins,

Polson

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To the residents of Lake County and the State of Montana, the question "Is there Lyme Disease in Montana?". The answer is "YES". Do our Doctors want to acknowledge it? "NO"

My daughter has had the symptoms for many years and no one has been able to figure it out. This is until our local Orthopedic doctor, to whom she was sent to by her attending physician, listened to her symptoms and decided to run a few more tests. After seeing all the tests that she has had were NORMAL, he wanted a few more tests but he was the only one that ever mentioned Lyme disease. She was sent to him because of her swollen ankle that hurt so bad she could barely walk on it and after x-rays showing that she had not broken it. She was told that the Orthopedics know more about joint problems. She had more blood work done, and only one came back POSITIVE, the one for Lyme. We finally got an answer. We questioned the test results but we were told that "tests don't lie". Her attending Physician put her on a month's worth of antibiotics and many other prescriptions and was told that would make her all better. So she went through a month of treatments and no difference and was told that it must have been a false positive and yet again it must be something else, because there is not Lyme here in Montana. He then ordered to run another panel of tests for Lyme again and they yet again came back positive. Until she got the final test results he prescribed her an anti depressant and that she must be just depressed and this would help with all her pain and she would be better, because she doesn't have LYME. She did not take it. After taking the antibiotics for 28 days, she developed Bells Palsy and went right in to see her doctor. He looked at her for a few seconds and said "yes, you have Bells Palsy, but that has nothing to do with Lyme and you do not have Lyme". She was given yet again antibiotics and steroids, and again, this was going to fix everything. After her physician saw the final test results she was told to go see an Infectious Disease doctor, he will give you answers. Mind you that her faith in doctors at this time is dwindling, being told you just need more vitamin D, or that you are just depressed, or that you must have RA, you have Lyme, you don't have Lyme and I could list more.

So off to see the nearest Infectious Disease doctor in Kalispell and time to get some real answers. He looked at her tests, asked her questions for an hour and a half and said, "I can't say you do have Lyme or don't have it." He will have to send her results to fellow panel of Doctors in Washington D.C. and see what they can come up with. While she waits for Doctors to decide what is wrong with her, she converses with a friend of hers, whom son went through the same thing with the doctors around here, he was diagnosed with Lyme too, and the only help they got was through a doctor in Bozeman. So my daughter sent her stuff there and within one day was called and told that she had a case of Lyme disease. The doctor wanted to see my daughter as soon as she could but that was not until late July. So the date came and away we go to Bozeman and after 2 hours of talking with the doctor and going over test results, we finally have answers and treatment with a regiment that will help her. Instead of being told that I am not sure what it is and hope I don't see you again.

While with this doctor we found out that my daughter is not the only case that she is treating in our area so far this year for Lyme, we found that very interesting.

There are probably people out there right now that have no idea what is wrong with them, and our local doctors don't either, and these people could be struggling with Lyme and don't even know it. It is sad that our local doctors don't want to say they don't know what is wrong with you when the tests they run come back normal but it is so clear that there is something wrong and they just chalk it up to being depression. For some of you out there that maybe in this same situation that my daughter went through, there is a great documentary out there called "Under Our Skin" to watch and gives you hope and lets you know that you are not crazy. If you have been diagnosed with Lyme just once, don't turn away from hope, it is out there. Don't give up.

As you may tell, as a mother of a child, I am not happy with local doctors on this subject and others that I have seen them try to fix in the past and chalk it up as the flu and later find out that this person really had cancer and only lived 2 months longer. It is very sad and discomforting. If you as a doctor doesn't know what is wrong, don't just prescribe something and send a person out the door. Send them to help and you may have to open up your eyes to the possibility that what shouldn't be happening here in Montana,it sure is.

I hope all who read this are more aware of Lyme Disease in our area and the reaction to it from our local attending doctors.

A very concerned Mother from Polson

MaryAnn Haskins

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Lyme disease divides experts: Great Falls family's journey with disease highlights struggle with controversial illness

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By David Murray | FILED UNDER - News / Local News | 4:50 PM, Mar. 11, 2013 | 0 Comments

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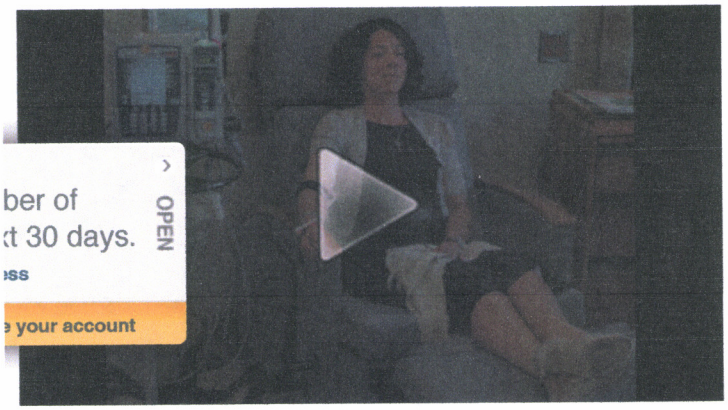

As the snow begins to melt in Montana, adult ticks emerge from hibernation and climb to the tips of low vegetation in search of their first blood meal. Ticks do not fly or jump but wait patiently for a warm body to brush past them. According to the Montana Department of Health and Environmental Sciences, they become aroused by the odor and breath of mammals, and transfer easily by stretching their legs toward the host. The consequences can be devastating.

In March 2010, Katy Peterson, now 31, began exhibiting symptoms of an odd illness that defied simple diagnosis.

"I broke out in hives and swollen joints, fatigue and vomiting — a lot of flu-like symptoms," Katy said from her home in Great Falls. "From there, it just progressively got worse. Other things came up like brain swelling. Sometimes I'm bedridden just because of the weakness, and then you also lose comprehension skills. Sometimes I can't read, sometimes I can barely balance my checkbook. I don't drive very often anymore."

Katy's illness continued without an accurate diagnosis for two years. Sometimes the symptoms would disappear for a week; sometimes she could barely get out of bed for days at a time. Her doctors were stumped, alternately theorizing she might be suffering from an allergic reaction, hiatal hernia, auto-immune disease or rheumatoid arthritis. She was prescribed steroids, antihistamines and anti-inflammatories. At least one doctor suggested she begin taking antidepressants.

When her illness reached a crisis point early in 2012, her family in Belt sent her to see a specialist in Seattle.

Shortly after examining her, Dr. Ralph Golan told Katy she had likely been exposed to Lyme disease and urgently pressed her to seek treatment for the chronic form of the disease.

Today, Lyme disease is one of the most divisive illnesses in American medicine. Virtually no aspect of this tick-borne illness is undisputed. Researchers, doctors and patient advocacy groups hotly debate Lyme disease's prevalence, diagnosis and treatment. Even the existence of chronic Lyme disease is disputed.

Emergence

Lyme disease is a tick-borne illness endemic to the northeastern United States and the western Great Lakes region. According to the Centers for Disease Control and Prevention, more than 33,000 confirmed or probable cases of Lyme disease were reported in the United States in 2011, though, because of misdiagnosis and underreporting, the actual number could be many times higher.

Early symptoms of the bacterial infection include a large bull's-eye rash, fever, headache and fatigue. Left untreated, it can spread to the joints, heart and nervous system, causing inflammation, meningitis and heart palpitations. In advanced stages, Lyme disease sometimes mimics other chronic illnesses like multiple sclerosis, Alzheimer's, Parkinson's and Lou Gehrig's disease. Today, Lyme disease is the most common vector-borne illness in the United States, but it was unknown to scientists just 35 years ago.

According to the National Institutes of Health, researchers noticed that an unusually large number of children in the area surrounding Lyme, Conn., were being diagnosed with juvenile rheumatoid arthritis in the early 1970s. Their symptoms typically started during summer and often included a skin rash just before the onset of joint inflammation. Many patients recalled having been bitten by a tick.

At the same time, 2,000 miles west at Rocky Mountain Laboratories in Hamilton, Mont., Swiss scientist Dr. Willy Burgdorfer was investigating the transmission of tick-borne illnesses to humans. In 1981, Burgdorfer isolated the bacteria responsible for Lyme disease in deer ticks that had been collected in New York state. For his work, Burgdorfer was nominated for a Nobel Prize in medicine, and the bacteria that causes the disease, Borrelia burgdorferi, was named in his honor.

Since then the disease has spread rapidly. Lyme disease has been reported in every state in the country except Hawaii, though the vast majority of cases remain confined to 13 states in the Northeast and Great Lakes regions. In the past decade, there has been a consistent occurrence of Lyme disease in the western coastal regions of California, Oregon and Washington, and a growing number of patients with Lyme disease are being diagnosed in eastern Canada and British Columbia.

For many years, Montana was one of a handful of states that had no confirmed cases of Lyme disease.

It wasn't until 2006 that the CDC confirmed a case of Lyme disease in the state. Since that time, the Montana Department of Public Health and Human Services (DPHHS) has reported an average of five cases a year of Lyme disease. The DPHHS and the CDC attribute all confirmed cases in Montana to people who traveled outside the area and contracted the illness in a recognized endemic state.

"There is virtually no risk of acquiring Lyme disease within the state of Montana," said Elton Mosher, disease specialist with the DPHHS. "We do not currently have the tick that is a competent vector for transmitting Lyme disease to humans. We entertain this kind of concern every year from people, especially in the northwest portion of the state, who swear up and down that they've got Lyme disease — and when we look at it more thoroughly, it's just not supported. We just do not have those ticks in Montana."

But like everything else about Lyme disease, where it can and cannot be contracted is disputed.

"I find it very troubling that any reputable organization could state that something like Lyme disease absolutely does not exist in a certain state," said Golan, a Lyme disease specialist and the physician who diagnosed Katy. "Lyme disease is carried by a tick and ticks attach to deer, attach to rodents, attach to birds, and these animals don't know where state borders are."

Katy and her family may never know with any certainty where she contracted Lyme disease. It is just the first in a whole list of confused and uncertain issues surrounding Lyme disease.

Detection

One of the greatest frustrations for Lyme's families like the Petersons is the general lack of public knowledge about Lyme disease and the reluctance of physicians to test for it. In a state that is listed as "Lyme disease free" it's difficult to get medical professionals to seriously consider Lyme disease as an option.

In the first year of Katy's illness, she and her husband, Jake, learned to expect doubt from most of the people they spoke to about it. Part of the problem was that she often had no clear outward appearance of being sick. The symptoms would come and go. On good days, she'd feel well enough to work hard at the couple's janitorial business. On bad days, she'd retreat to her sewing room, where she'd spend hours isolating herself from the people around her.

"I think, within our family and friends, there was a lot of doubt — like, 'Katy, get over it,'" she said.

It didn't help that doctor after doctor was unable to offer a conclusive answer as to what was ailing her.

"Over the course of this, we've went to every doctor we could and have had almost every test performed," Katy said. I was just a guinea pig. Nobody knew what was going on. We'd go to another doctor, knowing as we were sitting there that you're not going to get any help from them and you've just wasted another $500. I felt like they weren't even listening to what I had to say. It was like, 'We've got this young couple who doesn't got a clue.' That we were just these hypochondriacs."

"A lot of the symptoms she had — we'd look on the Internet and they came back as Lyme's," Jake Peterson said of his wife's illness. "We asked every doctor we went to and no doctor would even test us for it. Nobody would even hear it. 'That's crazy, there's no Lyme disease in Montana.'"

It's a common complaint expressed by many families who have struggled with Lyme disease. According to Golan, the problem is nested in the wide menu of symptoms that can be expressed by Lyme's, and in a medical community that is reluctant to recognize an illness that does not easily fit within accepted models of infectious disease.

"When I went to medical school, if a patient had more than seven symptoms, the professor said they needed to see a psychiatrist," Golan said. "These people are thought to be nut cases when in fact they've got a physical problem affecting many parts of their bodies. What makes it even harder is if the Lyme's happens to have an effect on their brain and they present psychiatric symptoms, then most doctors are reaching for their prescription pad for some tranquilizer or antidepressant or anti-anxiety agent."

The turning point came with a quick succession of events that began in early 2012. In January of that year, the Peterson's youngest son, Liam, then 2, began to exhibit symptoms similar to his mother's.

"When my son got sick, I knew exactly what was going to happen to him," Katy said. "He got the swollen joints, the rash. His knee swelled up to the size of a softball. We would be in the hospital with him, and I would tell the nurses, 'Look at this swollen joint, look at the rash — it's Lyme's.'"

Still the physicians demurred from ordering Lyme disease tests for either Katy or her son. Then Katy learned she was pregnant. The Petersons feared that the disease would afflict her unborn child, and they sought advice from Echoz Pregnancy Care Center in Great Falls.

"I went in there, and I just leveled with them," Katy recalled. "I have been sick, my son is sick, I am pregnant and I'm scared."

Echoz referred the Petersons to Dr. Stacy Kingsland, who agreed to test Katy for Lyme's. When the test returned, it did not conclude that she was currently infected with Lyme's, only that she had been exposed to the bacteria at some point.

In an odd respect, Katy could feel fortunate for this type of positive test result. In Montana, for a patient to be confirmed as being infected with Lyme disease requires they pass a four-tiered test.

"No. 1, they have to have the distinctive bull's-eye rash," Mosher said. "They have to have a history of a tick bite, they have to have traveled to an area where Lyme disease is endemic, plus they have to have lab confirmation."

Each one of these elements is somewhat problematic. According to a 2003 study by the CDC, as many as 30 percent of confirmed Lyme disease patients never exhibit any kind of rash at all, and in those patients who do, more than a third of the rashes are atypical and do not develop into the classic bull's-eye pattern. A significant percentage of Lyme disease patients, like Katy Peterson, do not recall being bitten by a tick, and the questions about where a patient can potentially contract Lyme disease have already been discussed earlier in this story.

"The only easy diagnosis of Lyme's is in those patients who walk in with a bull's-eye rash and who may have some of the clinical symptoms that go along with Lyme's," Golan said.

Confirmation of Lyme disease relies on laboratory testing, which is itself controversial. The Infectious Diseases Society of America (IDSA) and the CDC both recommend a two-tiered blood test for Lyme disease. Currently, there is no simple way to grow the bacteria that causes Lyme disease, as would be done when testing for other bacterial diseases like tuberculosis, pneumonia or staph infections. Instead, the first test for Lyme's disease looks for antibodies the body produces to fight the infection. If that test returns positive, then a second test is performed called the Western blot test, which detects proteins on the bacteria's surface.

The problem is that in the first weeks after infection, antibody tests are unreliable because the auto-immune system has not yet produced enough antibodies to be detectable. And, if the patient had been taking any antibiotics prior to the time of testing, that may hamper the accuracy of testing. Several studies have found that antibody tests for Lyme disease are correctly positive only about 65 percent of the time, and, without a positive antibody test, many doctors are reluctant to order the Western blot test, which, though more accurate, is expensive and technically difficult to perform.

Treatment

After testing positive for the Lyme's antibody, Katy was flown to Seattle to be examined by Golan. According to the Petersons, Golan was seriously concerned about Katy's health and recommended she immediately begin aggressive long-term antibiotic treatment, including having a catheter inserted to deliver medication directly to her heart.

Katy's pregnancy complicated her treatment options, however, and her Montana physician, Dr. Robin Thomson, recommended Katy receive only a low maintenance dose of antibiotics to inhibit the transmission of Lyme's to her unborn child. After the baby was born, Katy's antibiotic treatment could begin in earnest.

The type of treatment both Golan and Thomson have recommended for Katy is not endorsed by either the IDSA or the CDC. In fact, neither of these organizations recognizes chronic Lyme disease as a clinically proven illness, preferring instead to refer to lingering symptoms of fatigue, pain and joint or muscle inflammation as "Post-treatment Lyme Disease Syndrome" (PTLDS).

"Most medical experts believe that the lingering symptoms are the result of residual damage to tissues and the immune system that occurred during infection," a CDC public statement on Lyme disease says. "Regardless of the cause of PTLDS, studies have not shown that patients who received prolonged courses of antibiotics do better in the long run than patients treated with placebo. Furthermore, long-term antibiotic treatment for Lyme disease has been associated with serious complications."

The IDSA's guidelines for the treatment of Lyme disease (adopted by the CDC) call for oral antibiotics to be taken for 10 to 28 days. But a significant number of independent researchers and Lyme's disease patient advocacy groups say the IDSA's treatment guidelines are flawed, and that a one-month regimen of oral

antibiotics is insufficient to eliminate a bacteria that is slow-growing, burrows deep into tissues and can change its form and structure in response to antibiotic treatment.

"I believe, and the International Lyme and Associated Diseases Society (ILADS) believe that Lyme organisms can be alive and perpetuate problems for years, and one month of treatment doesn't even begin to address them," Golan said.

The credibility of IDSA's Lyme disease guidelines was seriously undermined in 2006 when it was revealed that a number of the doctors who authored these guidelines either cited their own research into Lyme disease to validate them or had connections to the pharmaceutical companies that develop and sell Lyme disease diagnostic tests. In 2008, the Attorney General's Office for the state of Connecticut announced an antitrust investigation into the IDSA's process for writing Lyme disease guidelines had found serious flaws.

"The IDSA's 2006 Lyme disease guideline panel undercut its credibility by allowing individuals with financial interests — in drug companies, Lyme disease diagnostic tests, patients and consulting arrangements with insurance companies — to exclude divergent medical evidence and opinion," said Attorney General Richard Blumenthal, now a U.S. senator.

In 2010, an independent review panel of nine scientists and physicians unanimously upheld the IDSA's 2006 treatment guidelines. But the damage already was done. Many researchers and patient advocacy groups continue to believe that the IDSA and CDC are compromised in their standpoint on Lyme's by a too cozy relationship with pharmaceutical and insurance companies.

During an interview in 2007, Burgdorfer, the discoverer of the Lyme disease bacteria and a scientist emeritus at the National Institutes of Health said, "I am a believer in persistent infections because people suffering with Lyme disease, 10 or 15 or 20 years later, get sick again. Because it appears that this organism has the ability to be sequestered in tissues, and it is possible that it could reappear, bringing back the clinical manifestations it caused in the first place."

"The controversy in Lyme disease research is a shameful affair," Burgdorfer went on to say. "And I say that because the whole thing is politically tainted. Money goes to people who have, for the past 30 years, produced the same thing — nothing. There are lots of physicians around who wouldn't touch a Lyme disease patient. They tell the nurse, 'You tell the guy to get out of here. I don't want to see him.' That is shameful. So this shame includes physicians who don't even have the courage to tell a patient, 'You have Lyme disease, and I don't know anything about it.'"

Toward wellness

In November 2012, Katy Peterson gave birth to a healthy baby girl named Lily. A few weeks after Lily's birth, Katy began long-term antibiotic treatment for her chronic Lyme disease. Progress has been slow. She still feels tired a great deal of the time. Sometimes her joints and muscles ache, and Katy still avoids crowds where she can become panicky.

"I just get too confused," she admitted. "The confusion and the chaos is too much — and then I'm worried about driving back."

Yet while the symptoms have not gone away, Katy and her family have two things they lacked since their journey through Lyme disease began two years ago — a clear understanding of the illness they face and hope that things will improve in the future.

"From the very beginning, I made a promise that I would not get stuck emotionally my illness, and that we would grow as a family despite my being ill," Katy said. "I could choose to be miserable, and sometimes I do chose to do that. But when it comes right down to it, the only real choice is to be hopeful."

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EXHIBIT 1
DATE 3/18/13
SB 296

Lyme Disease: Two Standards of Care

By Lorraine Johnson, JD, MBA
Executive Director, CALDA

Opinion within the medical community is deeply divided regarding the best approach for treating Lyme disease, particularly persistent Lyme disease that is not cured by short-term protocols. [1-3] This split has resulted in two standards of care. Both viewpoints are reflected in peer-reviewed, evidence-based guidelines. Some physicians treat patients for 30 days only and assume that remaining symptoms reflect a self-perpetuating autoimmune response. [4] Other physicians assume that the persistent symptoms reflect on-going infection and gauge the duration of treatment by the patient's individual clinical response. These physicians believe that there is insufficient evidence at this point to adopt standardized treatment protocols. [5]

While each viewpoint has a strong underlying hypothesis, the scientific evidence supporting either viewpoint is equivocal. Outcomes research is limited and conflicting. The NIAID has only funded three double-blind, placebo-controlled treatment outcome studies for long-term treatment of persistent Lyme disease. The findings of two studies (Klempner and Krupp) are contradictory, with one indicating that continued treatment is beneficial for treating fatigue and the other indicating that it is not.[6-8] The third NIAID-funded study has recently been completed and preliminary results support continued antibiotic treatment for patients with persistent Lyme disease.[9] The findings of five non-controlled studies support continued treatment.[1, 10-13] The existence of limited or conflicting controlled studies is not uncommon in the practice of medicine. When this is the case, of necessity the unique clinical course of the patient bears the laboring oar in treatment decisions.

Insurance companies have placed the full weight of their economic clout behind less expensive short-term treatment protocols. More expensive longer-term treatment options are discredited as "experimental" or "not evidence-based." The point, of course, is that the science underlying both the short-term and the longer-term treatment options is equally uncertain (similar to the situation with treatment of prostate cancer). The appropriate response to equivocal research findings in healthcare outcomes is to fund more research. It is estimated that only 20% of medicine practiced today is rooted in double-blind studies.[14] The bulk of medicine today is practiced in the grey zone. **Evidence-based medicine requires only that medicine be practiced in accordance with the evidence that currently exists, not that treatment be withheld pending research.**

Insurance companies have adopted guidelines based on short-term treatment approaches. **However, the legal standard of care for treating a condition is determined by the consensus of physicians who actually treat patients, not by treatment guidelines**.[15] Moreover, more than one standard of care may exist. A number of surveys have found a fairly even split among treating physicians in the case of Lyme disease: One survey found that 57% of responding physicians treat persistent Lyme disease for three months or more.[16] In another survey, "50% of the responders considered using antibiotics for a time greater than one year in a symptomatic seropositive Lyme disease patient. Almost that same number would extend therapy to 18 months if needed."[17] For treating early Lyme disease, there is conflicting evidence. Most physicians responding to one survey specified short-term treatment [18], while 43% of those responding to another survey would treat erythema migrans-positive Lyme disease for three months or more.[16]

When more than one standard of care exists, the critical question becomes *who* decides the appropriate course of treatment for the patient. Under the medical ethical principle of autonomy, the treatment decision belongs to the patient. Hence, the American Medical Association requires that the physician disclose and discuss with the patient not only the risks and benefits of the proposed treatment, but also the risks and benefits of available alternative treatments (regardless of their cost or the extent to which

the treatment options are covered by health insurance).[19] For example, patients with prostate cancer (where significant uncertainty exists regarding long-term treatment outcomes) must elect between watchful waiting, radiation and surgery. The legal doctrine of informed consent also requires that patients be advised of material treatment options. Treatment choices involve trade-offs between the risks and benefits of treatment options that only patients—who know the kinds of risks they are willing to run and the types of quality of life outcomes that matter to them—are uniquely suited to make. [20]

Respect for the basic autonomy of the patient is a fundamental principle of medical ethics. Without adequate information about treatment options, their probable outcomes, and the risks and benefits associated with each, patients cannot act autonomously. Today, however, many patients are either denied treatment by their HMO physicians who follow actuarial treatment protocols generated to keep treatment costs down, or they must find an independent physician to treat them, with the all but foregone conclusion that coverage for this treatment will be denied by their insurer based on cherry-picked (economically favorable) guidelines. Moreover, HMO physicians generally do not advise their patients that treatment alternatives exist.

Scientific uncertainty about Lyme disease has resulted in more than one treatment approach (like prostate cancer). We agree with the AMA, ACP and other professional medical organizations interested in promoting informed patient consent and want to make sure that:

- Physicians, insurers, patients and governmental agencies are educated that two treatment approaches exist;
- Physicians give patients sufficient information about treatment options to enable patients to make a meaningfully informed choice and respect the autonomy of that choice;
- Insurance reimbursement be provided for treatment rendered in accordance with either standard of care; and
- Government agencies provide unbiased information and remain neutral regarding both standards of care and treatment approaches.

EXHIBIT 1
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Lawmakers urged to intervene, protect doctors treating Lyme patients

By James Miller/State House News Service
Belmont Citizen-Herald
Posted Sep 22, 2009 @ 05:02 PM

Boston, Mass. —
With reported cases of tick-borne Lyme disease on the rise in Massachusetts, lawmakers heard impassioned and contradictory testimony Tuesday about whether the state should protect doctors who prescribe prolonged antibiotic treatment for the disease.

Massachusetts reported 3,960 confirmed cases of Lyme disease in 2008, according to the federal Centers for Disease Control and Prevention. That's a roughly 33 percent increase from 2007, when 2,988 cases were reported. The increase catapulted Massachusetts to second among U.S. states in the number of cases reported.

At issue Tuesday was a bill (H 1148) presented by Rep. Robert Hargraves (R-Groton) that would shield from disciplinary action doctors who prescribe long-term antibiotic therapy for Lyme disease-sufferers.

Similar legislation was signed into law in Connecticut this May.

Proponents, including the New Jersey-based Lyme Disease Association, say guidelines from the Infectious Diseases Society of America that recommend against long-term antibiotic treatment have become "de facto law," and many doctors won't buck them for fear of professional sanction or lawsuits.

"Doctors are not only fighting for their patients' lives; they're fighting for their professional lives," Hargraves said during a press conference before the hearing. He was joined by Rep. Jen Benson (D-Lunenburg), Rep. Kate Hogan (D-Stow) and Rep. Jeffrey Perry (R-Sandwich).

The Legislature's Public Health Committee heard from numerous advocates, including people who suffer from the disease and doctors who said the disease was under-diagnosed and its victims often receive insufficient care.

Committee members also heard from well-known doctors who urged them not to intervene — a move that would carve out a special niche for Lyme disease and limit the ability of Massachusetts health regulators to sanction doctors when needed. In testimony, some doctors were also critical of prolonged antibiotic treatment.

Transmitted by the blacklegged tick, Lyme disease typically leads to a non-itchy, red circle rash and fever and mild illness, according to the CDC. If not treated early, it can affect the nervous system, the heart, bones and joints, and lead to debilitation.

Proponents of Hargraves' legislation, which had about two dozen original sponsors, argued that incidences of Lyme disease often are misdiagnosed. And when they finally are identified, they require antibiotic attention much longer than the maximum 28 days recommended in the 2006 Infectious Diseases Society of America guidelines.

"It shouldn't be four weeks for a particular infection; it should be as long as it

takes, and that's a clinical decision that needs to be made," said Sam Donta, an internist with a specialization in infectious diseases and a retired professor of medicine at Boston University.

Donta said people who have had the disease for a year or two may need many months of antibiotic treatment.

In Massachusetts, many physicians won't provide that treatment because they "are intimidated because they're told that insurers won't cover the treatments, they'll be prosecuted if they go beyond these guidelines," Donta told the committee.

Mark Pasternak, chief of the Pediatric Infectious Disease Unit at Massachusetts General Hospital, offered a different perspective. He said there is no evidence that long courses of antibiotic therapy result in improved outcomes.

"Unfortunately many patients with persistent symptoms of fatigue or other nonspecific complaints seek out so-called Lyme-literate physicians who administer prolonged antibiotic therapies," said Pasternak, who also is president of the Massachusetts Infectious Disease Society.

Pasternack described those therapies as sometimes toxic, leading to serious complications, including blood-stream infections and antibiotic diarrhea and colitis.

His protestations weren't well received by some at the hearing. "I and so many thousands like me have been through so much," said Maureen O'Brien, a 50-year-old nurse from Westwood. "When is it going to stop?

She said she started suffering from classic neurological symptoms of Lyme disease 18 years ago.

After almost a decade of misdiagnosis and incorrect treatments, Donta identified her plight as Lyme disease, she said. She said prolonged antibiotic therapy made a huge difference, helping temper symptoms that have included vision and hearing loss, numbness, spinal cord damage and incontinence.

The committee was slated to discuss almost 20 bills Tuesday, dealing with a range of topics including the reporting of cases of autism, the testing of infants for Crabbe disease and creation of an insurer-backed vaccination trust fund.

There also was another Lyme disease bill, carried by Rep. Jennifer Callahan (D-Sutton.)

That bill calls for creation of a commission to study various aspects of Lyme disease and how it can be best dealt with in Massachusetts. Lawmakers have been on the brink of creating and funding such a commission before.

"I really believe Lyme disease is a silent epidemic in our state," Callahan said.

Read more: Lawmakers urged to intervene, protect doctors treating Lyme patients - Belmont, MA - Belmont Citizen-Herald
http://www.wickedlocal.com/belmont/news/x593048090/Lawmakers-urged-to-intervene-protect-doctors-treating-Lyme-patients#ixzz2KzYKKu81

EXHIBIT 1
DATE 3/18/13
SB 296

IDSA LECTURE

Counterpoint: Long-Term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease

Raphael B. Stricker
International Lyme and Associated Diseases Society, Bethesda, Maryland

(See the point by Auwaerter on pages 143–8)

Background. Controversy exists regarding the diagnosis and treatment of Lyme disease. Patients with persistent symptoms after standard (2–4-week) antibiotic therapy for this tickborne illness have been denied further antibiotic treatment as a result of the perception that long-term infection with the Lyme spirochete, *Borrelia burgdorferi,* and associated tickborne pathogens is rare or nonexistent.

Methods. I review the pathophysiology of *B. burgdorferi* infection and the peer-reviewed literature on diagnostic Lyme disease testing, standard treatment results, and coinfection with tickborne agents, such as *Babesia, Anaplasma, Ehrlichia,* and *Bartonella* species. I also examine uncontrolled and controlled trials of prolonged antibiotic therapy in patients with persistent symptoms of Lyme disease.

Results. The complex "stealth" pathology of *B. burgdorferi* allows the spirochete to invade diverse tissues, elude the immune response, and establish long-term infection. Commercial testing for Lyme disease is highly specific but relatively insensitive, especially during the later stages of disease. Numerous studies have documented the failure of standard antibiotic therapy in patients with Lyme disease. Previous uncontrolled trials and recent placebo-controlled trials suggest that prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms. Tickborne coinfections may increase the severity and duration of infection with *B. burgdorferi.*

Conclusions. Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with tickborne agents.

Lyme disease is a controversial illness [1–6]. The classic features of the disease include receipt of a tick bite followed by the so-called erythema migrans or "bullseye" rash and significant joint swelling typical of arthritis. Unfortunately, the classic features of this tickborne disease are not always present. For example, only 50%–60% of patients with Lyme disease recall having received a tick bite, and often the erythema migrans rash is absent or not in the shape of a bullseye [5, 6]. According to health departments around the United States, the typical bullseye rash is only reported in 35%–60% of patients with Lyme disease [7, 8]. Furthermore, frank arthritis is only seen in 20%–30% of patients with Lyme disease [1, 2]. Thus, the classic features of the disease may be absent, and the diagnosis may be easily missed [1–4].

In the absence of typical features of Lyme disease, patients may go on to develop a syndrome with multiple nonspecific symptoms that affect various organ systems, including the joints, muscles, nerves, brain, and heart. The myriad symptoms prompt the question whether this is "post–Lyme disease syndrome," a poorly defined entity triggered by Lyme disease, or whether these symptoms are caused by persistent infection with the Lyme spirochete, *Borrelia burgdorferi.* To address this question, we must first examine the pathophysiology of the disease.

PATHOPHYSIOLOGY OF LYME DISEASE

B. burgdorferi is a fascinating bacterium [9, 10]. It has >1500 gene sequences with at least 132 functioning

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genes. In contrast, *Treponema pallidum*, the spirochetal agent of syphilis, has only 22 functioning genes. The genetic makeup of *B. burgdorferi* is quite unusual. It has a linear chromosome and 21 plasmids, which are extrachromosomal strands of DNA. This is 3 times more plasmids than any other known bacteria (*Chlamydia* comes in a distant second, with 7 plasmids). Plasmids are thought to give bacteria a kind of "rapid response" system that allows them to adapt very rapidly to changes in the environment, and the complex genetic structure of *B. burgdorferi* suggests that this is a highly adaptable organism [9, 10].

In addition to its complex genetic makeup, *B. burgdorferi* engages in so-called "stealth pathology" to evade the human immune response [11–50]. Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic variation; physical seclusion; and secreted factors (table 1). These strategies are outlined below.

IMMUNOSUPPRESSION

During a tick bite and before transmission of the Lyme spirochete, tick saliva containing analgesic, anticoagulant, and immunosuppressive factors is expressed into the wound, allowing the spirochete to penetrate the skin and evade the local immune response [11–13]. *B. burgdorferi* also induces immunosuppression by complement inhibition and induction of inhibitory cytokines, such as IL-10. In addition, the bacterium induces monocyte and lymphocyte tolerization and antibody sequestration in immune complexes—all mechanisms of evading the immune response [14–19].

GENETIC, PHASE, AND ANTIGENIC VARIATION

B. burgdorferi engages in genetic, phase, and antigenic variation that shares various features with other organisms [20–23]. For example, gene switching is similar to what is seen with trypanosomes, mutation and recombination are typical of HIV, variable antigen expression is seen with *Neisseria* species, autoinduction of dormant organisms occurs in mycobacterial infection, and fibronectin binding occurs with staphylococcal and streptococcal infection.

B. burgdorferi may assume a dormant state with cyst formation [24–29]. Although spirochetal persistence in the cyst form is a controversial issue, it has recently been shown that neutrophil calprotectin can induce a dormant state in the spirochete, allowing it to persist in tissue without replicating and providing the means to avoid antibiotics [30].

Although antibiotic resistance associated with gene mutation was previously thought to be rare in *B. burgdorferi* infection [31], recent studies have demonstrated gene mutations in the Lyme spirochete that confer in vitro resistance to various antibiotics [32, 33]. The clinical implication of these gene mutations is uncertain at present.

PHYSICAL SECLUSION

The Lyme spirochete uses physical seclusion at intracellular sites as a means of evading the immune response in multiple cell types, including synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and neuronal cells [34–43]. In culture, *B. burgdorferi* can be grown in fibroblasts for >8 weeks, suggesting that the organism can thrive over long periods of time in the right place and under the right conditions.

Physical seclusion at extracellular sites, including the joints, eyes, and CNS, may also promote survival of the Lyme spirochete. In addition, *B. burgdorferi* engages in "cloaking" mechanisms by binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin. These substances can mask the bacterium and make it invisible to the immune system [38–42].

SECRETED FACTORS

There are a number of factors that are secreted either by *B. burgdorferi* itself or in response to infection with the spirochete [44–51]. For a number of years, it has been known that *B. burgdorferi* secretes a hemolysin, although its function is uncertain [44]. More recently, the spirochete has been shown to elaborate porin and adhesin, 2 proteins that allow bacteria to adhere to cells and pierce the cell wall to gain entry [45].

Even more recently, *B. burgdorferi* was found to secrete pheromones, including AI-2, which is also secreted by mycobacteria [46–50]. This is the first time that a spirochete has been shown to secrete an autoinducer and suggests that the Lyme spirochete engages in autoresuscitation like other dormant organisms, such as the tubercle bacillus [46–50]. In addition, *B. burgdorferi* can induce secretion of aggrecanase, an enzyme that damages cartilage [51]. This may be a mechanism by which the bacterium induces damage and inflammation in joints. Armed with these weapons of "stealth pathology," the Lyme spirochete is a formidable infectious agent.

LABORATORY TESTING

Let's turn briefly to laboratory testing in Lyme disease. A major problem is that current commercial Lyme serologic tests are not sensitive enough for diagnosis, especially during the later stages of disease [52–64]. The Centers for Disease Control and Prevention (CDC) advocates a "2-tier" testing system using an ELISA or immunofluorescence assay as a screening test, followed by a Western blot for confirmation if the result of the ELISA or immunofluorescence assay is positive. The CDC cautions, however, that the 2-tier system should only be used for surveillance purposes and not for diagnosis, and the reason for this warning is clear: although the 2-tier system has a very high specificity (99%–100%), thus avoiding the false-positive results that are the bane of surveillance statistics, it has relatively poor

Table 1. "Stealth" pathology of *Borrelia burgdorferi*.

Immunosuppression
Tick saliva components
Complement inhibition
Inhibitory cytokine induction (IL-10)
Lymphocyte/monocyte tolerization
Antibody sequestration in immune complexes
Genetic, phase, and antigenic variation
Gene switching (trypanosomes)
Mutation/recombination (HIV)
Variable antigen expression (*Neisseria* species)
Dormant state, autoinduction (*Mycobacterium* species)
Fibronectin binding (*Staphylococcus* and *Streptococcus* species)
Physical seclusion
Intracellular sites
Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)
Persistent infection in vitro (8 weeks)
Extracellular sites
Privileged sites (joints, eyes, and CNS)
Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)
Secreted factors
Hemolysin (BlyB)
Porin (Oms 28)
Adhesin (Bgp)
Pheromones (DPD/AI-2)
Aggrecanase (ADAMTS-4)

NOTE. See text for explanation and references.

sensitivity (50%–75%), which limits its use as a diagnostic test for individual patients.

Other problems with current Lyme disease testing include omission of highly specific bands from the commercial Western blot, sex differences in test reactivity, and limitations of molecular testing, and these issues have been discussed in detail elsewhere [1, 56, 60–63]. Thus, the diagnosis of Lyme disease remains problematic, with as many as one-half of patients experiencing failure with the current 2-tier testing approach [52–64].

TREATMENT OF LYME DISEASE

With this background concerning the clinical diagnostic problems, complex pathophysiology, and testing difficulties related to *B. burgdorferi*, we arrive at the topic of this debate, which is treatment failure in Lyme disease. Documented treatment failure with culture-confirmed *B. burgdorferi* infection was first reported >17 years ago by Preac-Mursic et al. [65], so it was surprising to see a quotation in the *New York Times* by 2 members of the Infectious Diseases Society of America (IDSA) Lyme disease guidelines committee stating that "[there] is no credible scientific evidence for the persistence of symptomatic *B. burgdorferi* infection after antibiotic treatment" [66]. Let's review the "credible scientific evidence" for persistence of this infection taken from articles published over the past 17 years.

ANIMAL MODELS

We can start with animal models of Lyme disease [67–75]. In the mouse, one study found that "persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for chronic or recurring Lyme disease" [67, p. 909]. In another study, "nine months after treatment, low levels of spirochete DNA could be detected by real time PCR in a subset of antibiotic treated mice" [68, p. 1430]. So at least in the mouse model, spirochetes may persist after appropriate treatment.

Next is the dog model—a particularly convincing model, because Straubinger et al. [69] revealed that, in dogs that had been experimentally infected with *B. burgdorferi* by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished persistent infection but failed to eliminate it. Furthermore, when dogs were observed for a 500-day postinfection period (the equivalent of 3–4 human years), *B. burgdorferi* DNA was detectable at low levels in multiple tissue samples obtained from the dogs, despite the administration of "adequate" antibiotic treatment [70].

Finally, in a model using our closest relative, the nonhuman primate macaque monkey, Pachner and colleagues [71–75] found that neurologic and cardiac disease were associated with persistent infection in these monkeys, and cytokine and gene expression related to persistent *B. burgdorferi* infection could be demonstrated >3 months after infection. In summary, these animal models provide "credible scientific evidence" for persistent infection in Lyme disease.

HUMAN STUDIES

Turning to human studies, there are a number of reports that show persistent symptoms of Lyme disease after short-term antibiotic therapy [76–96]. Persistent symptoms have been noted in 25%–80% of patients with Lyme disease after 2–4 weeks of antibiotic therapy [76–87]. Furthermore, infection that was determined to be persistent on the basis of either culture or PCR evidence has been documented in up to 40% of patients following receipt of the "adequate" antibiotic treatment recommended by the IDSA [88–96]. For example, positive culture and PCR results were found in synovium and synovial fluid specimens obtained from a patient 7 years after treatment [92], and a positive result was reported for a culture of an iris biopsy specimen obtained from a treated patient [93]. These reports suggest that short-term antibiotic therapy may suppress the Lyme spirochete but not eradicate it.

In another case, the patient's condition deteriorated despite receipt of repeated courses of antibiotic treatment over a 2-

Table 2. Results of placebo-controlled trials of antibiotic treatment in chronic Lyme disease.

Study	Year	Treatment	Results	Comments
Klempner et al. [101]	2001	IV Ctri for 4 weeks followed by oral doxycycline for 2 months vs. placebo	No improvement in fatigue or quality of life	Study was criticized because subjects had been sick an average of 4.7 years, and similar treatment had already failed; the treatment regimen was inadequate for degree of functional impairment [104]
Krupp et al. [102]	2003	IV Ctri for 4 weeks vs. placebo	SI in fatigue noted in 64% of treatment group, compared with 19% of control group; no improvement in cognition	The exact duration of illness was not stated (at least 6 months), and the treatment duration was relatively short; previously untreated patients fared significantly better than control subjects in terms of fatigue improvement (69% vs. 0%; $P<.01$)
Fallon [105]	2005	IV Ctri for 10 weeks vs. placebo	SI in cognitive and physical functioning at 12 weeks in treatment group, compared with control group	Improvement in physical functioning but not cognitive functioning was sustained in the treatment group at 24 weeks
Cameron [106]	2005	Oral amoxicillin for 3 months vs. placebo	SI in cognitive and physical functioning in treatment group, compared with control group	Treatment was successful in two-thirds of the patients who had the best initial quality of life, but it failed in one-third of the patients who had the worst initial quality of life

NOTE. IV Ctri, intravenous ceftriaxone; SI, significant improvement.

Table 3. Precedents for prolonged antibiotic therapy.

Disease	Organism	Treatment	Duration of treatment, months
Drug-susceptible tuberculosis	*Mycobacterium tuberculosis*	2–4 antibiotics	6–9
Multidrug-resistant tuberculosis	*M. tuberculosis*	3–5 antibiotics	18–24
Leprosy	*Mycobacterium leprae*	3–4 antibiotics	24
Atypical tuberculosis	*Mycobacterium chelonae*	Oral and intravenous antibiotics	6–12
Q fever endocarditis	*Coxiella burnetii*	2 antibiotics	36

NOTE. Data are based on [143–147].

year period. She received 12 months of intravenous antibiotic treatment, followed by 11 months of oral antibiotics, and her condition improved significantly [95]. Thus, this case report suggests that longer treatment may be beneficial in some patients with Lyme disease. Taken as a whole, these studies provide "credible scientific evidence" for persistence of *B. burgdorferi* infection after "adequate" short-term antibiotic treatment in humans.

That brings up the next question: does longer antibiotic treatment help in persistent Lyme disease? There have been a number of uncontrolled trials that support longer treatment of persistent disease symptoms [97–100]. The largest study included 277 patients who were treated with tetracycline for 1–11 months (mean duration, 4 months). The study showed that, after 2 months of therapy, 33% of patients had improvement in symptoms, but after 3 months of treatment, 61% of patients had decreased symptoms [97]. So this study suggests that longer treatment may result in better symptom outcome in Lyme disease. There have been other small, uncontrolled trials showing that longer treatment may have better symptom outcomes in patients with Lyme disease, including one trial that showed that patients who were re-treated with intravenous therapy had the greatest improvement in their symptoms [98–100].

In contrast to these uncontrolled trials, 2 randomized, placebo-controlled trials examined re-treatment of patients with persistent symptoms of Lyme disease (table 2) [101, 102]. Krupp et al. [102] studied 1 month of intravenous ceftriaxone, whereas Klempner et al. [101] studied 1 month of intravenous ceftriaxone followed by 2 months of oral doxycycline. The Krupp study showed improvement in fatigue with its 30-day treatment regimen, whereas the Klempner study showed no improvement in quality of life following re-treatment for 90 days. The main problem with these studies is that they included patients who had been symptomatic for an average of 4–5 years, and treatment with 1 month of intravenous antibiotics, with or without low-dose doxycycline, is insufficient for patients who have been sick this long [103, 104]. Thus, the generalizability of results in these highly selected patients with persistent Lyme disease is questionable [104].

In contrast to these studies, 2 placebo-controlled trials were presented in 2005 at the Columbia/Lyme Disease Association's annual meeting (table 2) [105, 106]. One study involved oral amoxicillin for 3 months versus placebo for previously treated patients, and re-treatment was successful for the two-thirds of patients with the best initial quality of life. A second study administered intravenous ceftriaxone for 10 weeks to patients with persistent neurologic symptoms of Lyme disease, and these patients had significant cognitive improvement with this treatment. We look forward to publication of these 2 placebo-controlled trials, which show that longer courses of antibiotic therapy are useful in patients with persistent Lyme disease.

COINFECTION WITH TICKBORNE AGENTS

In addition to infection with *B. burgdorferi*, tickborne coinfections are being recognized more frequently. If a patient is treated for Lyme disease and has symptoms that have persisted or worsened, the lack of improvement may be due to the presence of *Babesia, Anaplasma, Ehrlichia,* or *Bartonella* coinfection [107–126]. Coinfection with *Babesia* and *Ehrlichia* has been shown to exacerbate Lyme disease in mouse models [108–110] and also in humans [111–118]. Traditionally, *Babesia, Anaplasma, Ehrlichia* and *Bartonella* are thought to produce acute fulminant infections, but in fact these pathogens may cause low-grade infections that can increase the severity and duration of Lyme disease [119–125].

A disturbing study from New Jersey examined the prevalence of coinfections in *Ixodes* ticks that transmit Lyme disease [126]. In that study, the prevalence of *B. burgdorferi* infection was 33.6%, but the prevalence of *Bartonella* infection was 34.5%. Thus, *Bartonella* species were found more often than the Lyme spirochete in these ticks. This observation presages a greater problem with *Bartonella* infection associated with tick exposure in the near future.

TREATMENT APPROACH TO CHRONIC LYME DISEASE

What is the approach for a patient who presents with persistent symptoms of Lyme disease [127–140]? First, the Lyme Western blot should be repeated, and coinfection testing should be performed by a laboratory that is proficient in tickborne disease analysis. At the same time, other medical problems that could

cause persistent symptoms should be ruled out. Measurement of the CD57 natural killer cell level, which is an immunologic marker that can be used to monitor treatment in chronic Lyme disease, should be performed [129–131]. If neurologic symptoms are severe, a single-photon emission CT SPECT brain scan should be obtained, to see how much inflammation is present in the brain. Neuropsychiatric evaluation may also be helpful [132].

On the basis of these results, coinfections should be treated first, if any are present, and then oral or parenteral antibiotics should be used to treat symptoms of persistent Lyme disease. Antibiotic therapy should be administered in a rotating and open-ended manner, in conjunction with probiotics, to minimize adverse effects [133–136]. Monitoring of clinical symptoms, CD57 natural killer cell levels, and markers of inflammation should be performed in conjunction with treatment [137–140].

This approach differs from the recommendations of the current IDSA guidelines, which do not recognize persistent infection in chronic Lyme disease [141]. However, the treatment approach is consistent with the guidelines of the International Lyme and Associated Diseases Society, which mandates treatment for persistent infection in patients with chronic Lyme disease symptoms [142]. It is helpful to recall that *B. burgdorferi* shares certain pathophysiological features with mycobacterial infection and other chronic infections (table 1), that these infections may require prolonged antibiotic therapy (6–36 months), and that the risks of long-term treatment are considered justifiable in those situations (table 3) [143–147]. On the basis of the foregoing discussion, prolonged antibiotic therapy appears to be useful and justifiable in chronic Lyme disease.

In summary, >18,000 scientific articles have been written about Lyme disease. Some of these articles focus on the complex pathophysiology of *B. burgdorferi*, whereas others highlight the clinical uncertainty surrounding tickborne disease. Because the optimal therapy for this complicated illness is still in doubt, we must keep an open mind about the treatment of patients who present with persistent symptoms of Lyme and associated tickborne diseases.

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EXHIBIT 1
DATE 3/18/13
SB 296

LYMEPOLICYWONK: The CDC, the FDA and Lyme Disease Lab Tests: Two-Tiered Tests, IGeneX, the C6, and the New Culture Test
16th March 2013

The CDC website now states that before the CDC will recommend new tests, "their performance must be demonstrated to be equal to or better than the results of the existing procedure, and they must be FDA approved." But is FDA approval required for diagnostic tests? No, FDA approval is only required for tests that are marketed to other labs. Single lab tests, like those offered by IGeneX and Advanced Laboratory Services (ALS) do not require FDA approval. Instead, federal law requires that they undergo a rigorous validation process established by the Centers for Medicare and Medicaid Services (CMS) and Clinical Laboratory Improvement Amendments (CLIA). CMS and CLIA require developers to prove that their tests are accurate, precise, sensitive, and specific prior to marketing. Both IGeneX and ALS diagnostic tests are CLIA and CMS approved.

To pass CLIA, Lyme tests must demonstrate that they accurately detect positive samples of blood and test negative on control samples of blood. This is how these tests are validated. These samples are provided by the CDC—so there is no dispute that the samples are accurate. **Why is the CDC asking for more than compliance with federal regulations using CDC sample sets?**

And, what about its other requirement—that the test must be equal to or better than the existing two-tiered testing procedure recommended by the CDC. Research shows that the current two-tiered testing procedures do more harm than good. While the testing has few false positives (called "high specificity"), it has many false negatives (or "low sensitivity"). Two-tiered testing misses 44 of every 100 patients who have Lyme disease. Imagine if that were the case with AIDS! Take a look at the table below from the article "Let's Tackle the Testing":

Sensitivity and specificity of commercial two tier testing for Lyme disease

Study	Sensitivity	Specificity
Schmitz et al. *Eur J Clin Microbiol Infect Dis* 1993;12:419-24	66%	100%
Engstrom et al. *J Clin Microbiol* 1995;33:419-27	55%	96%
Ledue et al. *J Clin Microbiol* 1996;34:2343-50	50%	100%
Trevejo et al. *J Infect Dis* 1999;179:931-8	29%	100%
Nowakowski et al. *Clin Infect Dis* 2001;33:2023-7	66%	99%
Bacon et al. *J Infect Dis* 2003;187:1187-99	68%	99%
Mean of all studies	56%	99%

What plan do the CDC and NIH have for the future of testing? Well, the NIH has invested heavily in the C6 test. The C6 is commercially marketed by two companies, Immunetics and DiaSorin, both of whom have commercial ties with Dr. Wormser, who authored the IDSA guidelines which require positive lab tests for diagnosis. In addition, Immunetics receives NIH research grants, which fund Dr. Wormser's research. Dr. Barbara Johnson of the CDC and Dr. Gary Wormser, who authored the IDSA guidelines, have jointly published a number of articles supporting this test, which is FDA approved, but performs no better than the two-tiered strategy. **So, why is the American public funding C6 research?**

And, how do tests the CDC is targeting fare? The IGeneX test is called on in a CDC "warning" issued in February 2005 cautioning against tests that "interpret Western blots using criteria that have not been validated and published in peer-reviewed scientific literature." IGeneX test reports specify whether the test results meet the CDC interpretation criteria, which requires 5 of 10 IgG bands. However, other studies were able to increase the sensitivity of the test to 93% or higher by using an interpretation requiring 2 of 5 bands. So, IGeneX also reports this information. **Why is the CDC ignoring these studies which have a far greater sensitivity?**

What about the ALS culture test? The CDC surveillance criteria list "culture test" as an acceptable test, and culture tests are widely regarded as the "gold standard" of testing. As noted above, the ALS test has been validated using the CLIA and CMS requirements. However, it is a relatively new test. A recently published study of the test demonstrated that it had sufficient sensitivity and specificity, but these findings should be confirmed in additional studies. **Why isn't the government funding this type of research?**

It's time for the CDC and the NIH to abandon the failed two-tiered strategy and stop funding tests like the C6, which do no better. Patients want diagnostic tests with greater sensitivity so that patients can get diagnosed and treated. A recent article pegs the number of Lyme tests performed annually at 3.4 million—which translates into a market of roughly $340 million a year. Not only do these numbers suggest that there is a lot more Lyme around than the CDC or IDSA acknowledge, but they also tell us that commercially vested interests and the researchers they consult with may have a stake in keeping the status quo in lab testing regardless of how bad the tests are. **Could monetary considerations have something to do with opposition to new lab tests?**

The LYME POLICY WONK blog is written by Lorraine Johnson, JD, MBA, who is the Chief Executive Officer of LymeDisease.org, formerly CALDA. Contact her at lbjohnson@lymedisease.org.

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The American Association for Clinical Chemistry, which is a professional association of over 8,000 members concerned with blood

diagnostic tests, has an extensive website describing diagnostic lab test validation requirements. Interested readers should check it out.

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EXHIBIT 1
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A SUMMARY OF THE IDSA LYME EVIDENCE HEARING

On July 30, 2009, a newly formed panel from the Infectious Diseases Society of America (IDSA) heard 8 hours of testimony from 18 presenters representing various viewpoints on Lyme disease diagnosis and treatment. This was the first time the two sides of the Lyme controversy have been given equal time in front of a conflict-free evidence-review panel. And it's the first time that a medical guidelines hearing has been broadcast over the Internet for all the stakeholders to hear, from patients to researchers to treating physicians.
Over the past decade, two opposing camps have emerged in the battle over this tick-borne illness. One camp is represented by the group of 14 academic researchers who wrote the 2006 IDSA Lyme guidelines. They maintain that Lyme disease is 'hard to catch and easy to cure' because the infection is rare, easily diagnosed and cured with two to four weeks of antibiotics. This group claims that chronic infection by the Lyme spirochetal bacterium, *Borrelia burgdorferi,* is rare or nonexistent.

The opposing camp is represented by the International Lyme and Associated Diseases Society (ILADS), led by a group of community-based physicians. Its members argue that Lyme disease is not rare and tick bites often go unnoticed, especially since commercial laboratory testing for Lyme disease is inaccurate. Consequently, the disease is often not recognized and may persist in a large number of patients, requiring prolonged antibiotic therapy to eradicate persistent infection with the evasive Lyme spirochete.

This hearing came about as the result of an antitrust settlement initiated by Connecticut Attorney General, Richard Blumenthal in 2007. During his investigation, the Attorney General found substantial conflicts of interest among the 2006 panel members, who held commercial interests in diagnostic tests, vaccines, and insurance. In addition, he found that this panel had suppressed scientific evidence and had excluded opposing views from the panel.

After watching the entire hearing, my overall impression was that the community-based ILADS physicians gained significant ground in the evidence-based debate with the 2006 IDSA guidelines authors. The most compelling takeaway messages were:

1. THE GUIDELINES ARE TOO RIGID GIVEN THE STATE OF THE SCIENCE. The science on diagnosing and treating Lyme disease is still uncertain, and we need guidelines that allow physicians freedom to treat until this disease is better understood. Based on a national patient survey conducted by Lorraine Johnson of CALDA, it was found that 58% of Lyme patients remained ill after the IDSA's recommended treatment and 60% improved with longer courses

of antibiotics. Even though the IDSA Lyme guidelines are supposed to be voluntary, they are widely used by insurance companies to restrict physicians' ability to exercise clinical judgment, depriving seriously ill patients of the only available treatment option (long-term antibiotics) that can get them back to leading normal lives.

2. LONG TERM ANTIBIOTICS HELP SOME PATIENTS. A meticulous dissection of the 4 peer-reviewed studies used by the IDSA to deny longer courses of antibiotics showed that 2 of those studies had serious design flaws and the other 2 actually showed that patients improved after 6 weeks of IV antibiotics. Given that these 4 studies were based on a total of only 207 patients and a single antibiotic, it was clear that much more treatment research is needed. The other revision that most of the expert panelists seemed to back is Dr. Volkman's strongly held belief that the "two pill Lyme cure" recommended in the IDSA guidelines fails 80% of the time, and it should be removed from the guidelines. (Volkman Ph.D., M.D., is an Emeritus Professor of Medicine and Pediatrics at SUNY, Stony Brook.)

3. CHRONIC LYME IS CAUSED BY PERSISTENT INFECTION. Benjamin Luft, MD, from SUNY Stony Brook presented compelling evidence showing that the Lyme bacteria can persist in the body beyond the IDSA-recommended 2 to 4 weeks of antibiotics. He cited the Barthold (UC Davis) mouse study and other studies that demonstrated the multiple strategies that the organism uses to escape detection by the immune system. Overall, the weigh of evidence for the existence of chronic Lyme far outweighed the IDSA "expert opinion" that the symptoms that linger beyond treatment are due to a "medically unexplained symptom" (MUS), labeled as "Post-Lyme Syndrome" by the IDSA authors.

4. MORE ACCURATE TESTS ARE NEEDED. Dr. Ray Stricker, as well as a number of other presenters, showed that the two-tier surveillance Lyme test system endorsed by the IDSA, though highly specific, lacks the sensitivity required for an accurate diagnostic test, missing 88 out of every 200 Lyme patients. This results in thousands of Lyme patients being misdiagnosed and undercounted. (The CDC admits that U.S. Lyme cases are being underreported by 6- to 12-fold each year.) The CDC spokesperson, Barbara Johnson, Ph.D., however, stood by these tests, even though the expert panel seemed shocked that the CDC's endorsement was based on a decade-old study that looked at a mere 26 patients.

During the hearing, the 9 expert reviewers listened intently and asked many astute questions. This panel will now spend a few months assessing all information submitted before and during the hearing to determine whether the existing guidelines should be maintained, modified or entirely rewritten. The panel expects to complete its review by the end of the year.

Although I'm optimistic that anyone listening to all eight hours of testimony will see the urgent need to rewrite the guidelines in a major way, I worry that the

officers and lawyers running this commercially-driven medical society may water down the conclusions to protect the society from lawsuits. All of the panel's conclusions could be reversed if the IDSA officers assign a biased team of writers to execute the recommendations.

Three days after the hearing, my worst fears were realized when the IDSA President, Anne Gerson, M.D., said this, as if the hearing never happened:

"The physicians and scientists who wrote the Infectious Disease Society of America's (ISDA) guidelines thoroughly reviewed all the medical evidence and took great care to address the claims made by the small minority of physicians who advocate long-term antibiotic use."

"The notion that the authors had financial conflicts of interest is absurd to anyone who has read the guidelines, which recommend generic tests and a short course of generic drugs."

As the researcher for UNDER OUR SKIN who spent years uncovering the invisible conflicts of the 2006 IDSA guidelines authors, my conclusion is that the battle over these guidelines is not over conflicts surrounding the cure – a prompt course of off-patent antibiotics. (A curative dose of doxycycline or amoxicillin can be purchased at Walmart for $4.)

This conflict is all about a small group of academic researchers controlling every aspect of a disease for profit. They ignored or creatively interpreted new scientific data to protect their lucrative revenue streams from vaccine trials, arthritis/lupus/fibromyalgia clinical trials and government grants.

My impressions of the hearing and hopes for a happy ending were summed up nicely by Lorraine Johnson, the champion of the Lyme patients who organized much of the ILADS evidence:

"This hearing shows that the weight of the science falls on the side of providing patients with treatment options. The speakers supporting the 2006 guidelines relied heavily on conjecture, belief and reputation, advancing an unsubstantiated somatic disorder hypothesis for possible explanations of why patients remain ill. Hypothesis, conjecture and beliefs are not science and hopefully this panel will recognize that and gut these guidelines."

And here is my favorite quote of the day, which came from Dr. Ken Liegner, a Lyme-literate physician from Armonk, New York:

"This is a formidable pathogen. We should be humble before this disease."

Finally, on a possibly hopeful note, the IDSA just requested from Open Eye Pictures nine copies of UNDER OUR SKIN which will be given to each of the panelists. In addition, we offered to screen the film and speak with it at the October IDSA conference in Philadelphia. Though we're skeptical this will

happen, we're happy and humbled that the film is proving its potential to affect policy and people's lives.

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Congressional Record
111th Congress (2009-2010)

ISSUES REGARDING LYME DISEASE -- (Extensions of Remarks - September 29, 2010)

[Page: E1872] GPO's PDF

SPEECH OF
HON. CHRISTOPHER H. SMITH
OF NEW JERSEY
IN THE HOUSE OF REPRESENTATIVES
WEDNESDAY, SEPTEMBER 29, 2010

- Mr. SMITH of New Jersey. Madam Speaker, as chair of the congressional Lyme Disease Caucus and a person who has been closely involved in Lyme disease issues for over twenty years, I want to bring to your attention extremely troubling issues regarding Lyme disease.

- Lyme disease is the most common of all vector-borne infections in the U.S., with approximately 290,000 new cases in 2008. With the increase in Lyme cases, problems due to poor diagnostics and ineffective treatments for Lyme disease have become almost overwhelming--affecting larger numbers of people over longer periods of time.

- Many patients are angry because progress in addressing Lyme disease has been impeded by entrenched bias and a lack of accountability in the science of tick borne diseases. It is critical that we identify biases and impediments that are constraining the science on Lyme and to open up the dialogue to honest and transparent debate. The scientists who have long been marginalized, the treating physicians who have felt intimidated and threatened, and most importantly the sick patients and their families need our help.

- My main purpose here today is to introduce for inclusion in the *Congressional Record* the following statement ``The Patient Perspectives on the Research Gaps in Tick Borne Diseases,'' written by three of the Nation's largest Lyme disease advocacy organizations, who represent tens of thousands of patients. I believe that this statement provides important perspectives that need to be heard and taken to heart.

PATIENT PERSPECTIVES ON THE RESEARCH GAPS IN TICK BORNE DISEASES
(Submitted by Time for Lyme, the national Lyme Disease Association, and the California Lyme Disease Association on behalf of our patients across the United States)

In December 2009, Labor HHS 2010 appropriations language, signed into law by President Obama, encouraged the National Institutes of Health (NIH) to ``sponsor a scientific conference on Lyme and tick-borne diseases ..... the conference should represent the broad spectrum of scientific views ..... and should provide a forum for public participation and

input from individuals with Lyme disease." The language also requires NIH to identify research gaps to understand the ``mechanisms of persistent infection." The passage of this language represents a significant opportunity to summarize and solidify the issues that prevent scientific progress for a disease recognized here for 35 years, if, and only if, this process occurs without bias. Progress can be accomplished if the stewards commit to the elimination of predisposition by key decision makers.

It is not clear why the NIH elected to subcontract this issue to the Institute of Medicine (IOM), given that the existing NIH conference structure contains the best process to address the appropriations language requirements. According to the NIH Consensus Development Program, which explains the two relevant types of conferences offered by NIH, ``when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen." This conference format would appropriately address the research gaps that exist for Lyme and tick-borne diseases as it provides a ``snapshot in time" of the state of knowledge on the conference rather than a policy statement of the NIH or the Federal Government.

In Lyme disease, there are two distinct disease paradigms, each providing science to support its claims. One paradigm views the disease as ``hard to catch and easy to cure" and denies the existence of chronic Lyme disease--persistent infection with Borrelia burgdorferi, the spirochete that causes the disease. Under this paradigm, the state of the science for patients with chronic Lyme disease is closed. Any treatment is considered too risky because practitioners are unable to determine the cause or extent of patient symptoms, or they view the symptoms

as insignificant and write off the patients' complaints as psychiatric in nature. This leaves seriously ill patients without any viable therapeutic avenues. It also shuts the door on future research necessary to get patients to a state of wellness.

The alternative paradigm says that the science is too unsettled to be definitive and there can be one or more causes of persistent symptoms after initial treatment in an individual who has been infected with the agent of Lyme disease. These causes include the possibility of persistent infection, or a post-infectious process, or a combination of both, with the Lyme bacterium itself driving the autoimmune process. This paradigm allows doctors the ability to exercise their clinical judgment and provide therapies that are helping their patients.

Patients with Lyme disease need a research agenda that reflects outcomes that matter to patients, namely effective diagnostic tools and effective treatments that restore them to health. The reason there are two disease paradigms in Lyme disease is because central pieces of the puzzle are missing or are inadequate. The first area of concern involves testing.

There are no reliable biomarkers of the disease.\1\ Current diagnostic tests commonly used do not detect the spirochete that causes Lyme disease, rather, they detect only whether the patient has developed antibodies to the pathogen. Antibody production, if it registers on the tests at all, takes weeks to appear, thus rendering the current tests ineffective in the earlier and more easily addressed stage. Additionally, the Lyme antibody has been shown to form a ``complex" with the bacterium itself--and tests cannot detect ``complex" antibodies. Once triggered, antibody reactions may remain long after an infection has been treated, also clouding the diagnostic and treatment picture.

The two-tier testing system endorsed by the Centers for Disease Control and Prevention (CDC) is very specific for Lyme disease (99%), so it gives few false positives. But the tests

have a uniformly low sensitivity (56%)--missing 88 of every 200 patients with Lyme disease. By comparison, AIDS tests have a sensitivity of 99.5%--missing only one of every 200 infected patients.\2\ Sensitive AIDS tests were developed less than 10 years into the disease, while archaic Lyme tests remain unreliable 35 years later. There is a critical need for research exploring newer technologies such as polymerase chain reaction (PCR), which is used with many other diseases, and cutting-edge proteomics. Strain variations and co-infections with other organisms, often transmitted by the same tick bite, obscure the diagnostic picture further.

A vast number of strains of Borrelia burgdorferi have been identified. Variation in strain may cause differing symptoms or severity of symptoms as well as determine the appropriate antibiotics and duration of treatment needed to clear the infection.\3\ Different strains may also express different proteins. Preliminary research shows that proteins need to be examined to find the ones most often expressed, then using microarray technology, doctors may be able to diagnose patients using a chip which contains the proteins.

Research is needed concerning the role of mutation on persistence. Some research indicates that bacteria can exchange genetic material, probably contributing to its ability to invade different systems in the body--some may have a proclivity for the heart muscle, others for the brain, and some for muscles and joints. By exchanging genetic material, bacteria may be able to form a symbiotic relationship to avoid detection by the immune response or to further invade the body.

To date, every NIH-funded treatment research study has been designed using the inaccurate diagnostic test results as part of the entry criteria. The entry criterion in these studies excluded the vast majority of Lyme patients and created sample sizes too small (less than 220 patients to date) to detect clinically important treatment effects or generalize to the clinical population. Moreover, Lyme has not attracted industry funding for treatment approaches, which places the disease at a considerable research disadvantage. To detect clinically relevant treatment effects requires much larger treatment trials with sample populations that reflect those seen in clinical practice.\4\

One thing that past research has demonstrated is that patients with Lyme are a heterogeneous population. Hence, the course of illness and responsiveness to treatment may vary depending on the duration of onset of the disease to its diagnosis and treatment, the presence of co-infections, comorbid factors, other genetic characteristics of the patients, and the virulence of the strain(s) with which the patient is infected. Research sample populations must reflect those seen in clinical practice to yield clinically relevant results.

As advised by the Appropriations language, research on the pathophysiology of Lyme disease is necessary. Research projects need to be designed which determine the course of the disease from inception, and which utilize treatments that effectively interfere with the mechanisms that allow the infection to persist. Little to no government sponsored science has been dedicated to the effects on persistence of the different forms of the Lyme bacterium (cyst vs. flagellar), the role, if any, of biofilms, sequestration of the organism from the immune system, the exchange and mutation of genetic material of the spirochete, and the role that components of the bacterial genome may play in protecting it from eradication by the immune system or antibiotics. Understanding the pathology of the organism can greatly enhance targeted diagnostics and treatment modalities.

Patients also need studies that explore a range of treatment options. The ideal antibiotics, route of administration, and duration of treatment for any stage of Lyme disease are not established. No single antibiotic or combination of antibiotics appears to be capable of completely eradicating the infection in all patients, and treatment failures or relapses are reported with all current regimens, although they are less common with early aggressive

treatment.\5\ Treatment failure rates suggest the need to re-examine the effectiveness of the currently recommended monotherapy as a treatment approach. Studies need to explore combination treatments and longer term treatment regimens, which have been critical to the successful treatment of AIDS and tuberculosis.

Patients need the type of outcomes research advocated by the IOM to examine how well treatments are working in actual clinical practice.\6\ While not all patients with chronic Lyme disease have returned to a state of wellness, many have, and we need to find out how and why. This information can then be applied to other patients and used to establish a research agenda for treatment that has a likelihood of success, rather than abandoning patients based on limited treatment trials.

The IOM process does not allow these research ideas to be heard in an unbiased and transparent fashion with balanced divergent viewpoints. While the NIH process precludes bias on the part of panel members, the IOM does not. Four of the six members of the IOM panel that have been selected belong to IDSA, a medical society that has a known bias against chronic Lyme disease diagnosis and treatment. Rather than providing curative treatments that restore health, the IDSA would provide costly and long term palliative treatments, presumably for life. While the NIH requires participation by major stakeholders (including patients and treating physicians), the IOM does not.

The summary of the IOM proceedings will reflect this pervasive lack of objectivity, undermining its integrity and credibility. Additionally, much IOM deliberation is done behind closed doors and an anonymous panel will be permitted to comment on the written record. Because of such flaws in the IOM proceedings, the three largest patient interest groups who were offered a brief opportunity to speak (TFL) at the IOM October 2010 meeting and an opportunity to provide a commissioned paper--CALDA, the LDA and TFL--pulled out of the conference in protest.

From a research perspective, strongly held paradigms can create a closed loop, and experiments may be designed, implemented and interpreted to support a particular viewpoint.\7\ The antidote to bias is to balance scientific perspectives and to ensure that all scientific viewpoints are being heard and explored. Given the extraordinary stream of federal funding granted to researchers who support the closed paradigm which was created and is supported by the Infectious Diseases Society of America (IDSA) and their vested interest in maintaining the status quo, it is not reasonable to expect this group of researchers to serve as neutral arbiters of scientific debates over competing scientific paradigms. For example, Lyme related panels dominated by IDSA have time and time again excluded opposing viewpoints from participating or controlled the review process to ensure outcomes that reinforce the IDSA paradigm. If past is prologue, it is obvious what the future holds for panels dominated by one group.

Worse, the small treatment trials that have been conducted have been given an undue amount of weight by IDSA researchers and in its guidelines and used to apply a degree of certainty on the science that far exceeds the limitations of the small sample sizes of the studies. Further, they claim that the state of the science is sufficient to determine with certainty that chronic Lyme disease does not exist, is not treatable with antibiotics, and that no further research on this topic is needed. Sample size affects the strength of the conclusions that may be drawn from them: ``Providing definitive answers in the face of low event rates and small-to-moderate treatment effects necessitates sample sizes in the thousands or tens of thousands. ..... Funding for such mega-trials is very limited, and is often restricted to industry sources." \8\

For that reason, the Connecticut Attorney General antitrust investigation into the development process of IDSA Lyme guidelines found exclusionary practices and suppression

of divergent viewpoints on the part of IDSA panels that crafted IDSA 2000 and the 2006 Lyme disease guidelines. Although IDSA settled the investigation with the Attorney General by agreeing to review its guidelines with a panel without conflicts of interest, the control of the process was in the hands of IDSA, which again selected a panel consisting almost exclusively of IDSA members and excluding treating physicians who held divergent viewpoints.

It was patients who pressed for the language in the Appropriations bill that called for a review of the state of the science of Lyme disease. However, patients need that process to occur in a transparent manner, without bias, and with the participation of all stakeholders. Albert Einstein defined insanity as ``doing the same thing over and over again and expecting different results.''

This process is a perfect example of that insanity.

Patients want research which will restore their health. Their voice and the voice of the clinicians must be given the necessary weight to legitimize the research agenda and the research process. Truth in science can be achieved through open debate in an independent process free from bias and conflicts of interest. The scientific process fails when one side of a debate controls the arena and sets the rules to ensure that its viewpoint prevails.

Lorraine Johnson, JD, MBA, Chief Executive Officer, California Lyme Disease Association.

Patricia V. Smith, President, Lyme Disease Association, Inc.

Diane Blanchard/Deb Siciliano, Co-Presidents, Time for Lyme, Inc. ENDNOTES

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\2\ Stricker RB, Johnson L. Lyme wars: let's tackle the testing. BMJ 2007; 335:1008.

\3\ Weintraub P. What we don't know about Lyme. Experience Life Magazine June 2009.

\4\ Guyatt GH, Mills EJ, Elbourne D. In the era of systematic reviews, does the size of an individual trial still matter. PLoS Med, 2008; 5:e4.

\5\ Hunfeld KP, Ruzic-Sabljic E, Norris DE, Kraiczy P, Strle F. In vitro susceptibility testing of Borrelia burgdorferi sensu lato isolates cultured from patients with erythema migrans before and after antimicrobial chemotherapy. Antimicrobial agents and chemotherapy 2005; 49:1294-301.

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\8\ Guyatt GH, Mills EJ, Elbourne D. In the era of systematic reviews, does the size of an individual trial still matter. PLoS Med, 2008; 5:e4.

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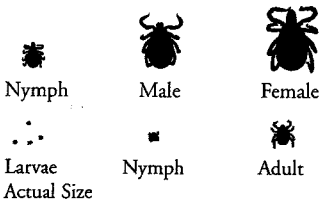
Tick Identification Guide

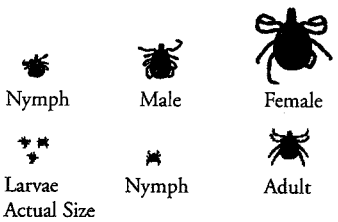
Ixodes scapularis
(includes deer tick)

Transmits agents of: Lyme, babesiosis, anaplasmosis, tick paralysis, Powassan encephalitis.
Possibly transmits: tularemia, bartonella.



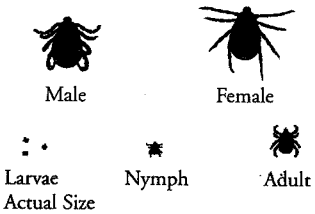
Amblyomma americanum
(includes lone star)

Transmits agents of: ehrlichiosis, STARI (southern tick-associated rash illness), tick paralysis, tularemia.
Possibly transmits: Rocky Mt. spotted fever.



Dermacentor variabilis
(includes American dog tick and wood tick)

Transmits agents of Rocky Mt. spotted fever, tick paralysis, tularemia.
Possibly transmits: ehrlichiosis. Although a small percentage of dog ticks carry the Lyme bacteria, no transmission has been proven.



Photos: James L. Occi MA, MS

Major Tick-Borne Diseases

Lyme Signs & Symptoms

EM (bull's eye) rash at bite site (less than 50%), other types of rashes, rash at other than bite site, flu-like illness. Musculoskeletal: joint/muscle pain in feet, swelling in toes, balls of feet, ankle pain, burning in feet, shin splints, joint pain or swelling, stiffness of the joints, neck or back, muscle pain or cramps that may migrate, neck creaks and cracks, neck stiffness, TMJ. Reproductive: testicular pain / pelvic pain, menstrual irregularity, milk production (lactation), sexual dysfunction or loss of libido. Cardiac/Pulmonary: chest pain or rib soreness, shortness of breath, heart palpitations, pulse skips, heart block, heart murmur or valve prolapse. Neurological: twitching of the face, eyelids or other muscles, headache, tingling, numbness, burning or stabbing sensations, facial paralysis (Bell's palsy), dizziness, poor balance, increased motion sickness, light-headedness, wooziness, difficulty walking, tremor, confusion, difficulty in thinking or with concentration or reading, forgetfulness, poor short term memory, disorientation (getting lost, going to wrong place), difficulty with speech, double or blurry vision, eye pain, blindness, increased floaters, increased sensitivity to light or sound, buzzing or ringing in ears, ear pain, deafness, seizure activity, white matter lesions, low blood pressure. Neuropsychiatric: mood swings, violent outbursts, irritability, depression, disturbed sleep (too much, too little, early awakening), personality changes, obsessive/compulsive disorder, paranoia, panic/anxiety attacks, hallucinations. Gastrointestinal: nausea or vomiting, difficulty eating, change in bowel function (constipation, diarrhea), gastritis, abdominal cramping, irritable bladder or bladder dysfunction, cystitis. Other: fever, sweats, or chills, weight change (loss or gain), fatigue, tiredness, hair loss, swollen glands, sore throat, difficulty swallowing, swelling around the eyes.

Other Tick-Borne Diseases

One tick bite can give you many different diseases at the same time (co-infections). Treatments vary, examples provided as information only.

Babesiosis - Protozoan, babesia microti, WA-1, MO-1; sometimes fatal in elderly or those without spleen. Symptoms include fever, chills, fatigue, headache, muscle pain, sweats & anemia.

Bartonella-illness - Bartonella henselae or other spp., can be transmitted by cat bite/scratch or tick bite when atypical presentations may result including visual problems, headaches, enlarged lymph nodes, resistant neurological deficits, new onset of a seizure disorder. Diagnosis by acute and convalescent antibody titers (IFA) and by PCR (DNA) analysis.

Support for this project has been provided by Rotary International

Ehrlichiosis - Human monocytic ehrlichiosis caused by Ehrlichia chaffeensis (symptoms below).

Anaplasmosis - caused by Anaplasma phagacytophilum. Symptoms of both ehrlichiosis and anaplasmosis include fever, malaise, headaches, chills, severe muscle aches, vomiting, anemia, lung infection, decreased white blood cells and platelets, elevated liver enzymes, seizures, encephalopathy, meningitis, confusion, ataxia, and cranial nerve palsy. Death can result.

STARI (southern tick-associated rash illness) - A Lyme-like disease transmitted by lone star tick, may get rash, other early Lyme symptoms, no test available.

Rocky Mountain Spotted Fever - Caused by the bacterium Rickettsia rickettsii. Symptoms include headaches, myalgia, and a characteristic rash usually beginning on wrists, ankles, palms, soles.

Tularemia - Caused by a bacterium, Francisella tularensis, Symptoms include headache, chilliness, vomiting, aching pains, fever. Infection site develops into an ulcer, swollen glands, sweating, weight loss, debility.

Powassan Encephalitis - Caused by a flavi virus, Powassan (POW). May possibly be transmitted by Ixodes scapularis. Symptoms usually begin suddenly 7-14 days following infection, and include headache, fever, nausea and vomiting, stiff neck, and sleepiness. Later, breathing distress, tremors, confusion, seizures, coma, paralysis, and sometimes death can occur.

Twyst of Lyme
Promoting Lyme Disease Awareness
www.twystoflyme.org
twystoflyme@gmail.com
529 Moose Hollow Rd
Victor, MT 59875

Tick Identification Guide

Ixodes scapularis
(includes deer tick)

Transmits agents of: Lyme, babesiosis, anaplasmosis, tick paralysis, Powassan encephalitis.
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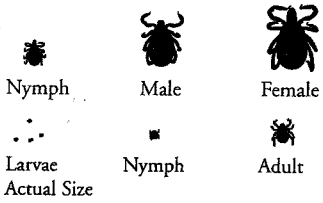

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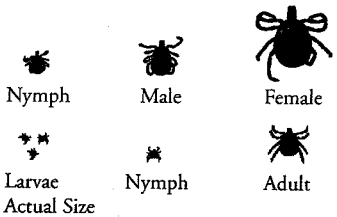

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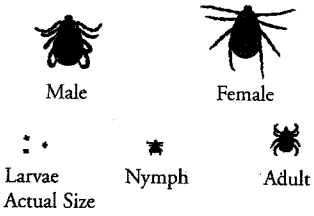
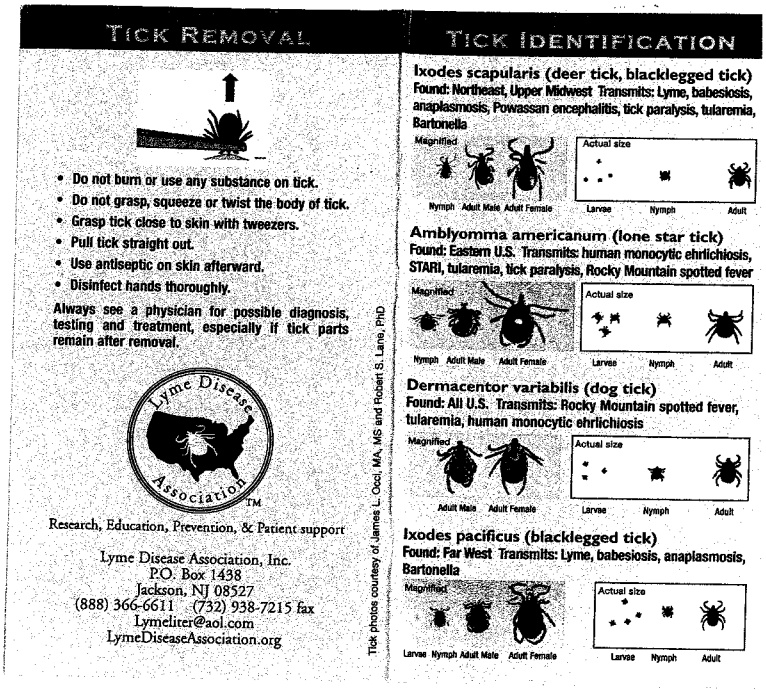


Photos: James L. Occi MA, MS



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LDA
Lyme Disease Association
Funding research projects from coast to coast

> Is a national, all-volunteer 501(c)(3) corporation. Contributions are tax deductible to the extent allowed by law.
> Contributes 98 cents of every dollar donated to programs.
> Provides input for federal and state Lyme legislation.
> Helps children with Lyme get a proper education.
> Sponsored first national medical conference focusing on Lyme disease in children & adolescents.
> Partnered with Time for Lyme & Columbia University to open the Lyme & Tick-Borne Diseases Research Center to study cronic Lyme.
> Has LymeAid 4 Kids for kids w/o insurance.

Affiliates/Chapters/Coalitions:

Time for Lyme, TFL (CT)
California Lyme Disease Association, (CALDA)
Lyme Disease Network of New Jersey, Lymenet.org
Lyme Association of Greater Kansas City, LAGKC (KS/MO)
Lyme Disease Association of Southeastern Pennsylvania
NYC Lyme Disease Support Program (NY)
Texas Lyme Disease Association, TLDA (TX)
Florida Lyme Advocacy, Inc.
Harford Co. LDSG, Inc. (MD)
Minnesota Lyme Action Support Group
Oregon Lyme Disease Network
Mid Shore Lyme Disease Association, Inc. (MD)
Lyme Disease Association Southeastern Florida Chapter
Lyme Disease Association Eastern Connecticut Chapter
Lyme Disease Assn. Corning/Fingerlakes Area Chapter (NY)
Lyme Disease Association, Cape Cod Chapter (MA)
Lyme Disease Association, Pennsylvania Chapter (LDAPAC)
Lyme Disease Association, Rhode Island Chapter, LDARIC
Stop Ticks on People, STOP (NY)

Other suggested resources:

http://Columbia-Lyme.org
http://www.LymeNet.org
http://www.IGeneX.com
http://www.ILADS.org

Lyme & Pets

> Dogs, cats, horses, and cows can get Lyme disease and other tick-borne diseases and can be tested.
> Perform tick checks to protect your pets.
> Use veterinarian recommended products.
> Dogs - symptoms are unexplained lameness, fever, lethargy, loss of appetite.
> Cats - symptoms are excessive sleep, fever, appearing arthritic or lame, stop eating.

Tick Identification Guide

Ixodes scapularis (deer tick)
Found in Northeast & Upper Midwest

Transmits agents of: Lyme, babesiosis, anaplasmosis (aka human granulocytic ehrlichiosis), Powassan encephalitis, tick paralysis, tularemia, bartonella.

Ixodes scapularis have been shown to carry ehrlichiosis (HME), but to date, transmission is still in question.

MAGNIFIED

Nymph Adult Male Adult Female

ACTUAL SIZE

Larvae Nymph Adult

Amblyomma americanum (lone star)
Found throughout the United States

Transmits agents of: human monocytic ehrlichiosis, STARI (Southern tick-associated rash illness), tularemia, tick paralysis, Rocky Mountain spotted fever, Q fever.

MAGNIFIED

Nymph Adult Male Adult Female

ACTUAL SIZE

Larvae Nymph Adult

Dermacentor variabilis (American dog)
Found throughout the United States

Transmits agents of: Tick paralysis, Rocky Mountain spotted fever, tularemia, human monocytic ehrlichiosis.

Although a small percentage of dog ticks carry the Lyme bacterium, no transmission has been proven.

DOG TICK

MAGNIFIED

Adult Male Adult Female

ACTUAL SIZE

Larvae Nymph Adult

Dermacentor andersoni (wood)
Found in Rocky Mt. States & SW Canada

Looks similar to American dog tick (above)

Transmits agents of: Rocky Mountain spotted fever, tularemia, Colorado tick fever, tick paralysis, Q fever.

Ixodes Pacificus (western black legged)
Found in West

Transmits agents of: Lyme, babesiosis, anaplasmosis (aka human granulocytic ehrlichiosis), bartonella.

Ixodes pacificus have been shown to carry ehrlichiosis (HME), but to date, transmission is still in question.

Larvae Nymph Adult Male Adult Female

Larvae Nymph Adult

Endorsed by:

ILADS

International Lyme & Associated Diseases Society
A Medical and Research Organization for Health Science Professionals
www.ILADS.org

The following companies have supported publication of this educational material:

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Insect Shield® Repellent Technology
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Tick photos thanks to James L. Occi, MA, MS & Robert S. Lane, PhD

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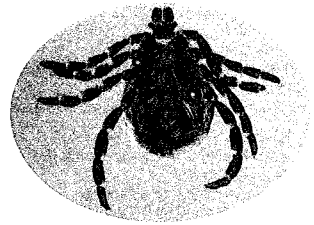
Lyme R Primer



Learn About Lyme & Other Tick-Borne Diseases

- Lyme Disease
- Anaplasmosis
- Babesiosis
- Ehrlichiosis
- Bartonella
- Rocky Mountain Spotted Fever
- Tularemia

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(LDA)
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Toll-free info (888) 366-6611
Fax (732) 938-7215
E-mail: Lymeliter@aol.com
Website: www.LymeDiseaseAssociation.org

Tick Removal

> Do not burn or use any substance on tick.
> Do not grasp, squeeze or twist body of tick.
> Grasp tick close to skin with tweezers.
> Pull tick straight out.
> Use antiseptic on skin.
> Disinfect tweezers.
> Wash hands thoroughly.
> Always see a physician for possible diagnosis, testing and treatment.
> Improper tick removal increases chances of infection.

Tick Testing for Lyme, Babesia, Anaplasma, Bartonella & Ehrlichia

> Save tick alive if possible.
> Place in airtight container or zip lock bag.
> Put in with moist cotton ball (no alcohol).
> Send with check to tick-testing lab.

Tick testing labs include:

IGeneX Labs, Palo Alto, CA (800) 832-3200
MDL, Mt. Laurel, NJ (877) 269-0090
NJ Labs, New Brunswick, NJ (732) 249-0148
Check your state/local health department

Prevention

> Perform frequent, thorough tick checks.
> Wear light-colored clothes.
> Tuck pants into socks.
> Put clothes in dryer for 30 minutes to kill ticks.
> There are products containing DEET for skin.*
> There are products containing Permethrin for clothes.*
> There are clothes which protect against ticks* www.rynoskin.com

** Always follow manufacturer's directions. The LDA does not make specific product recommendations or grant any warranties.*

Get the Facts

> You can contract many tick-borne diseases simultaneously from the same tick bite.
> You can test negative and still have Lyme disease.
> The longer a tick attachment, the greater risk of disease transmission.
> According to the CDC surveillance critera, an erythema migrants (EM) rash in an endemic area, means Lyme disease – in a nonendemic area, rash requires a positive test.
> CDC criteria are for surveillance purposes, not diagnosis.
> Not everyone who contracts Lyme disease gets a rash.
> Lyme is a clinical diagnosis based on a patient's symptoms, history and examination.
> Lyme bacterium can cross the placenta into the fetus, can cause death of the fetus, and its DNA can be found in breast milk.
> Lyme patients often get worse before getting better on treatment (Jarisch-Herxheimer reaction).
> Lyme symptoms can develop days or months after a tick bite.
> Lyme can cause death occasionally.

A scanning electron microscope image of Borrelia burgdorferi penetrating a human B cell (in vitro), at a magnification of approximately 89,000.
Photo Credit: David W. Dorward, Ph.D. NIH Rocky Mountain Labs, MT.

Lyme Bacteria:Borrelia burgdorferi

> Go intracellular & hide; go dormant and also mutate.
> Become sequestered in difficult to penetrate sites (central nervous system, joints, eyes).
> Use body's own cells to shield them.
> May have other than spirochete forms such as L-form cell wall deficient) and cystic form (giant L-body) which are not readily treatable with antibiotics and whose functions are not clearly understood.
> Have been found in patients after long-term treatment.
> May be associated with a neurotoxin.

Lyme Signs & Symptoms

EM (bull's eye) rash at bite site (less than 50%), other types of rashes, rash at other than bite site, flu-like illness. **Musculoskeletal:** joint/muscle pain in feet, swelling in toes, balls of feet, ankle pain, burning in feet, shin splints, joint pain or swelling, stiffness of the joints, neck or back, muscle pain or cramps that may migrate, neck creaks and cracks, neck stiffness, TMJ. **Reproductive:** testicular pain / pelvic pain, menstrual irregularity, milk production (lactation), sexual dysfunction or loss of libido. **Cardiac/Pulmonary** chest pain or rib soreness, shortness of breath, heart palpitations, pulse skips, heart block, heart murmur or valve prolapse. **Neurological:** twitching of the face, eyelids or other muscles, headache, tingling, numbness, burning or stabbing sensations, facial paralysis (Bell's palsy), dizziness, poor balance, increased motion sickness, light-headedness, wooziness, difficulty walking, tremor, confusion, difficulty in thinking or with concentration or reading, forgetfulness, poor short term memory, disorientation (getting lost, going to wrong place), difficulty with speech, double or blurry vision, eye pain, blindness, increased floaters, increased sensitivity to light or sound, buzzing or ringing in ears, ear pain, deafness, seizure activity, white matter lesions, low blood pressure. **Neuropsychiatric:** mood swings, violent outbursts, irritability, depression, disturbed sleep (too much, too little, early awakening), personality changes, obsessive/compulsive disorder, paranoia, panic/anxiety attacks, hullicinations. **Gastrointestinal:** nausea or vomiting, difficulty eating, change in bowel function (constipation, diarrhea), gastritis, abdominal cramping, irritable bladder or bladder dysfunction, cystitis. **Other:** fever, sweats, or chills, weight change (loss or gain), fatigue, tiredness, hair loss, swollen glands, sore throat, difficulty swallowing, swelling around the eyes.

Tests for Tick-Borne Diseases

Lyme Disease Tests:

> **Antibody Response** - tests only the level of antibody produced by your body in response to the disease. Includes: ELISA, C6Peptide, IgG and IgM Western Blots. During the first year after a tick bite, less than 65% of patients produce antibodies, and they may not last. By year two, less than 50% of patients still have an antibody response. Antibody response tests are most effective starting 4-12 weeks after a tick bite, and accuracy rates vary considerably. Antibody levels may be negative after inadequate treatment with antibiotics.
> **Antibody Capture** - an antibody test with the same problems as the test above.
> **Culture** - grows actual organism. Difficult to do, but when positive, it is considered confirmatory for Lyme.
> **Antigen Capture** - a highly defined antibody captures pieces of the Lyme organism. Actually checks for the presence of a piece of Lyme bacteria and supports the diagnosis of active infection. Includes LDA (Lyme Dot Antigen Assay for Urine and CSF).*
> **Polymerase Chain Reaction (PCR)** - checks for the actual presence of the genetic material (DNA/RNA) of the organism. If the sample contains any DNA/RNA, the PCR is highly accurate. Can be performed on all tissues of the body.*

Babesiosis, Bartonella & Ehrlichiosis Tests:

> **Babesia** - an IFA (IgG & IgM), FISH (Flourescent in-situ Hybridization) and PCR may be ordered.*
> **Ehrlichia** - an IFA and PCR for E. equii (HGE) and/or E. chaffeensis (HME) and PCR for HGE and HME are available.*
> **Bartonella henselae** - an IFA and PCR are available.*

** These tests were developed and performance characteristics determined by independent labs. They have not been cleared or approved by the FDA; however, the FDA has determined such clearance is not necessary. They are designed for clinical purposes and should not be regarded as investigational or for research.*

Other Tick-Borne Diseases

One tick bite can give you many different diseases at the same time (co-infections). Treatments vary, examples provided as information only.

> **Babesiosis** - Malaria-like illness caused by a protozoan, *babesia microti*, WA-1, MO-1, sometimes fatal in the elderly or those with no spleen. May be more severe in patients with coexisting Lyme. Symptoms include fever, chills, fatigue, headache, muscle pain, sweats and anemia. Treatment may be atovaquone with azithromycin or clindamycin and oral quinine.
> **Bartonella-illness** - disease caused by *Bartonella henselae* or perhaps other spp. that can be transmitted either by a cat bite or scratch or a tick bite. When tick-borne, atypical presentations may result including visual problems, headaches, significant lymph node enlargement, resistant neurological deficits, and the new onset of a seizure disorder. Diagnosis is made by acute and convalescent antibody titers (IFA) and by PCR (DNA) analysis. Treatment may be tetracycline and quinolone.
> **Ehrlichiosis** - Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis* (symptoms below Anaplasmosis).
> **Anaplasmosis** - Formerly human granulocytic ehrlichiosis, is caused by *Anaplasma phagacytophilum*.

Symptoms of both ehrlichiosis and anaplasmosis include fever, malaise, headaches, chills, severe muscle aches, vomiting, anemia, lung infection, decreased white blood cells and platelets, elevated liver enzymes, seizures, encephalopathy, meningitis, confusion, ataxia, and cranial nerve palsy. Co-infection with Lyme can cause more severe symptoms. Death can result. Treatment is with doxycycline.

> **Rocky Mountain Spotted Fever** - Caused by the bacterium *Rickettsia rickettsii*. Symptoms include headaches, myalgia, and a characteristic rash usually beginning on wrists, ankles, palms and soles. Treatment is tetracycline.
> **Tularemia** - Caused by a bacterium, *Francisella tularensis*, Symptoms include headache, chilliness, vomiting, aching pains, fever. Infection site develops into an ulcer, swollen glands, sweating, weight loss, debility. Treatment, streptomycin or gentamicin.
> **Powassan Encephalitis** - Caused by a flavi virus, Powassan (POW), transmitted by the *Ixodes cookei, Ixodes marxi, Ixode spinipalpus*, and *Dermacentor andersoni* ticks. May possibly be transmitted by *Ixodes scapularis*. Symptoms usually begin suddenly 7-14 days following infection, and include headache, fever, nausea and vomiting, stiff neck, and sleepiness. Later, breathing distress, tremors, confusion, seizures, coma, paralysis, and sometimes death can occur.
> **Q Fever** - Caused by Coxiella burnetti. Acute symptoms include hepatitis and peneumonia or chronic endocarditis.

Lyme Disease & Education: It's the Law

All states have their own special education laws; two federal laws protect students with Lyme disease and supercede state code and regulations. Individuals with Disabilities Education Act (IDEA) covers all students who have some form of disability. Students with chronic Lyme may fit several different categories depending on how severe the disease has impacted the child's ability to profit from regular education. Read your state's special education code to become an active participant in the decision making process for your child. Many states have slightly different categories and definitions than those given in IDEA. Remember IDEA supercedes all state special education laws except when the state law is more protective of your child's rights or offers more services.

Nationally, students with chronic Lyme often are classified and have an IEP, or they may qualify under Section 504 for a 504 plan. Anyone who has a physical or mental impairment that substantially limits one or more major life activities (e.g., walking, learning, working) or has a record of having a substantial impairment or is regarded as having a substantial impairment is entitled to placement in the regular educational environment with the use of supplementary aids and services, unless it is demonstrated that education in the regular environment cannot be satisfactorily achieved. Locally, check state law and school district special education policies. New Jersey law requires school districts to annually inservice staff members who teach students with Lyme disease. For more information, go to **www.504idea.org** and **www.idea.org**

EXHIBIT 1
DATE 3/18/13
SB 296

Specializing in Lyme Disease and Associated Tick-Borne Diseases

Over 20 Years Experience

What Is Lyme Disease?

Lyme disease is a world-wide infectious disease caused by microscopic bacteria carried by tiny ticks.

B. burgdorferi, a spiral bacteria that causes Lyme disease, seen through a microscope.

How Is Lyme Transmitted?

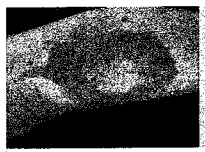
There are several species of deer ticks across the US that become infected with the spiral bacterium, Borrelia burgdorferi. Unsuspecting humans and animals walking through woodlands and brushy areas may be bitten by a tick and never know it. The tiny ticks, some the size of poppy seeds, may stay on your body for hours to days. The tick engorges itself with blood. If infected, the spirochete is transmitted to the bloodstream of the person or animal during the bite.

What If I Suspect Exposure?

Early recognition is important. If you find a tiny tick attached to your skin, if you were in a known tick-infested area, or if you have symptoms described herein, see your physician.

What Are The Symptoms?

A characteristic red bulls-eye rash (EM) at the site of the bite is present in less than 40% of patients. The rash may appear within days to weeks after the bite, but could be hidden in hairline or underarms.



EM RASH - Rashes from other bacteria in the tick may show up immediately. Typically, the rash from Lyme bacteria appears days or weeks after the bite.

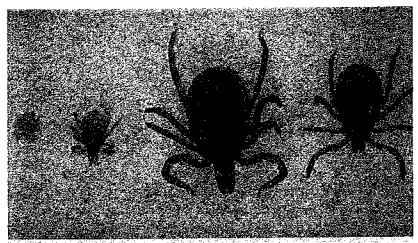
Some patients report flu-like symptoms, fever, aches, fatigue, neck stiffness, jaw discomfort, muscle pain and stiffness, swollen glands, and red eyes. Symptoms may appear, disappear and reappear at various times. Nervous system abnormalities include memory loss and partial facial paralysis (Bell's palsy). Migratory joint pains, and pains in the tendons, muscles and bones may occur later in the disease. Arthritic symptoms, if present, usually affect the large joints like the knees.

How Is Lyme Disease Diagnosed?

Lyme disease is a clinical diagnosis. This means that the physician makes the diagnosis using your clinical history and symptoms. If a physician observes an EM rash, a diagnosis of Lyme disease will be made. If a rash is not seen by a physician, laboratory tests are often needed to help with the diagnosis.

Can Ticks Be Tested?

Not all ticks are infected with the spiral bacterium, B. burgdorferi. If the tick was saved, it can be tested by our laboratory for the presence of the Lyme bacteria using a test called PCR. We also test ticks for Babesia, Ehrlichia, Bartonella henselae and Rickettsia (Rocky Mountain Spotted Fever). These pathogens are also carried by ticks. A Tick Test Request Form is available on our website.



From left to right: Larvae, Nymph, Female, Male Tick. Tick in Nymph stage is the size of a poppy seed.

Are There Other Tick-Borne Diseases?

The same tick that carries the bacteria that causes Lyme Disease, can also carry other pathogens. The most common are Babesiosis, Ehrlichiosis, Bartonellosis and Rickettsiosis (Rocky Mountain Spotted fever). It is estimated that up to 25% of the ticks that cause Lyme disease may transmit one or more of these other diseases. Babesiosis is like malaria with the symptoms of acute disease being fever, chills, vomiting and fatigue. It is usually self-limiting except in Lyme patients and those who have undergone splenectomy. There are two forms of Ehrlichiosis: Anaplasma phagocytophila (HGA) and HME (Human Monocytic Ehrlichiosis). HGA is primarily on the East coast, upper Midwest and California. HME is primarily in the Southeast, lower Midwest and Southwest, with cases reported in CA, NJ, NY, and WI. These acute diseases may have symptoms of fever, chills, vomiting and fatigue and require prompt antibiotics. Subclinical forms of these diseases may be present in patients with Lyme disease.

Miscellaneous Testing

IGeneX, Inc. offers the CD57* test and Chlamydophila pneumoniae IgG* and IgA* as part of our testing menu. CD57 natural killer (NK) cells can be very low in patients with chronic diseases and the levels of CD57 NK cells usually increase if treatment is successful. Therefore, the CD57 test can be used to monitor patients on therapy. In patients with low CD57 counts, Lyme disease and C. pneumoniae infection should be included in differential diagnosis.

C. pneumoniae can cause acute respiratory disease, but it can also persist in some patients with chronic respiratory conditions and cardiovascular disease.

What Tests Are Available?

A variety of tests is available. Many doctors who are unfamiliar with Lyme disease just use the Lyme test available in their local laboratory. This is usually the Lyme ELISA. This test measures a patient's anti-body, IgM and/or IgG, s in response to exposure to the Lyme bacteria. By today's standards, these tests are not very sensitive. IGeneX, Inc. will only perform the ELISA test in conjunction with Western Blots.

The LYME IFA (performed as part of a Lyme Panel) detects IgG, IgM and IgA antibodies against B. burgdorferi. IgM-specific titers usually persist in the presence of disease. Antibody levels tend to rise above background levels about 2-3 weeks after infection and may remain elevated in case of prolonged disease.

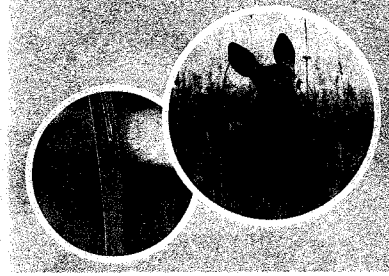
The WESTERN BLOT tests (IgG and/or IgM) visualizes the exact antibodies you are making to the Lyme bacteria. In some cases, the laboratory may be able to say that your "picture of Lyme antibodies" is consistent with early disease or with persistent and/or recurrent disease. Not all patients have anti-bodies at all times when tested. Antibodies are more commonly detected within the first year after infection, although re-infection may cause a significant rebirth of antibodies. At most, only 70% of patients have antibodies early, and the presence of antibodies alone does not make a diagnosis of disease.

The LYME DOT BLOT ASSAY (LDA) looks for the presence of pieces of the Lyme bacteria in urine. The assay specificity is better than 90%.

The PCR (Polymerase Chain Reaction) Test, a highly specific and sensitive test, detects the presence of the DNA of the Lyme bacteria. The PCR test is often the only marker that is positive in all stages of Lyme disease. The test can be performed on blood, serum, urine, CSF and miscellaneous fluids/tissues. Unfortunately, Lyme bacteria like to "hide" in the body, therefore, PCR can often be negative. Studies performed on different sample types suggest that performing PCR on multiple sample types improves assay sensitivity. In the Lyme Panels, PCR on whole blood is performed as a courtesy when PCR on serum is ordered. This gives the panel 80% sensitivity.

For patients with clinical symptoms of Lyme disease who test negative by the IFA Screen or IgG/ IgM Western Blots, the PCR on serum and whole blood, or the LDA/Multiplex PCR Panel on urine may be appropriate. There are physician developed antibiotic protocols to enhance the sensitivity of the LDA. In addition, there seems to be increased sensitivity of this test during the start of menses.

IGeneX



Which Test Is Best?

Lyme disease is very complicated to diagnose because:

- Lyme bacteria are not always detectable in the whole blood, even in active disease. The bacteria like to hide.
- Every patient responds differently to an infection.
- Antibodies may only be present for a short time.

Lyme Disease Tests

- IgG/IgM/IgA Screen (IFA)*
- IgG/IgM and IgM Antibody ELISA
- C6 Peptide
- IgG Western Blot and IgM Western Blot
- 31 kDa Epitope Test*
- Lyme Dot Blot Assay (LDA)*
- Multiplex PCR for urine, whole blood, serum, CSF
- Multiplex PCR for Miscellaneous samples (ex. Skin biopsy,breast milk)*

In addition to Lyme disease, a co-infection may be suspected for Babesiosis, Ehrlichiosis, Bartonellosis or Rickettsiosis. We offer tests for these other tick-borne illnesses. The tests are IFA (Immunofluorescent assay) or direct tests by PCR. In the case of Babesia, we offer a screen for B. microti and B. duncani (West Coast strain). In addition, we offer a Babesia FISH and Bartonella FISH (Fluorescent In Situ Hybridization) test that detects parasites/bacteria directly on air-dried blood smears. The FISH test is highly specific for the organism unlike the standard test, the geimsa stain smear, which is neither sensitive nor specific.

Babesiosis Tests

- B. microti IgG/IgM Antibody
- B. duncani IgG/IgM Antibody*
- Babesia PCR Screen
- Babesia FISH (RNA)

Ehrlichiosis Tests

Anaplasma phagocytophila (HGA):

- IgG/IgM Antibody
- PCR

Human Monocytic Ehrlichia (HME):

- IgG/IgM Antibody
- PCR

Bartonellosis Tests

- B. henselae IgG/IgM Antibody
- Bartonella PCR
- Bartonella FISH*

Rickettsiosis Tests

- Rickettsia rickettsii/typhi IgG Antibody
- Rickettsia PCR (Only R. rickettsii PCR will be reported for NY residents*)

*Not yet available for NY Residents

Central Nervous System Tests

Patients with neurological symptoms of Lyme disease may need to have a spinal tap in order to study "the blood of the brain," the CSF (cerebral spinal fluid). These patients may have negative blood and urine tests and show positive results with CSF. The LDA and PCR can be performed on CSF, as well as specific DNA tests for Bartonella henselae and Rickettsia.

How To Order Tests

LYME PANELS have been put together to provide cost savings to the patient when more than one test is ordered. The Panels are listed on our Patient Test Requisition Form, including Co-Infection Panels for certain regions of the country you live in or may have visited. This information can be found on our website at www.igenex.com.

How Can Lyme Disease Be Prevented?

Wear long sleeve shirts and long pants when going into tick country. Light colors are best so ticks can be easily seen. Tuck pants into socks and spray the clothes with a known tick repellent. After being in an area known to harbor ticks, check skin and all hair areas thoroughly. Remove ticks promptly. Check pets carefully, they are a source of entry for ticks into the house. Deer hunters need to spend extra time checking their gear before bringing it into autos and homes.

How Do You Remove A Tick?

1. Use tweezers or forceps.
2. Grasp the tick mouthparts close to the skin.
3. Avoid squeezing the tick, which may spread infected body fluids.
4. Pull the tick straight out. Do not twist. Do not attempt to burn the tick.
5. Save the tick (you may want to have it tested for B. burgdorferi or other tick-borne diseases).
6. Wash your hands with soap and water.
7. Apply antiseptic to bite site.

What Is The Treatment ?

It is reported that Lyme disease can be treated successfully with antibiotics if caught early in the infection. Prevention is the best cure for infection. Patients whose disease is caught late often need to be on antibiotics for longer periods of time. There is controversy among physicians as to the length of treatment. ILADS physicians' feel treatment should continue for 2 months after patient's symptoms improve. Ehrlichiosis is often treated with many of the same antibiotics used for Lyme disease. Babesiosis is often treated with Mepron and Zithromax. Many physicians believe that they need to treat the Babesiosis before treating Lyme disease to achieve clinical success.

For any questions regarding this information or inquiries on testing at IGeneX, please contact Customer Service at 800-832-3200. You may also contact us at customerservice@igenex.com.

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What You Should Know About Lyme Disease

IGeneX Inc.

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Evidence of Persistent Infection

Evidence of persistent infection notwithstanding previous antibiotic treatment is strong. *B. burgdorferi* have been cultured from patients who have been given intensive, 21 days to one year, antibiotic therapy with IV third generation cephaloporins. A summary of some of the peer-reviewed medical research demonstrating persistence of *B. burgdorferi* is set forth in the table below.

Laboratory Confirmed Infection with *Borrelia burgdorferi* (Bb) Despite Antibiotic Treatment	
Study	**Comments**
Battafarano et al. 1993[1]	Patient with chronic septic Lyme arthritis of the knee for 7 years, despite multiple antibiotic trials and synovectomies. Bb documented in synovium and synovial fluid.
Bayer 1996[2]	97 patients who had been treated with antibiotics for extended periods of time and had symptoms of chronic Lyme were PCR-positive.
Bradley et al. 1994[3]	Two previously treated Lyme patients with PCR-positive synovial fluid.
Breier et al. 2001[4]	Despite treatment with four courses of ceftriaxone, "[s]pirochaetes were isolated from skin cultures obtained from enlarging LSA lesions.... [S]erology ... was repeatedly negative."
Haupl et al. 1993[5]	Repeated antibiotic treatment necessary to stop the progression of disease but did not completely eliminate Bb from all sites of infection. Bb cultured from ligament sample.
Lawrence et al.[6]	Patient's CSF was positive for complexed anti-*B. burgdorferi* antibodies, *B. burgdorferi* nucleic acids and free antigen despite aggressive antibiotic therapy.
Liegner et al. 1993[7]	11 months later, after treatment, T-cell stimulation test with *Borrelia burgdorferi* antigens were strongly positive. A year later, paired serum and CSF samples were strongly positive.
Masters 1995[8]	Patient treated for six months; then relapsed and *Borrelia burgdorferi* was cultured from blood.
Nocton et al. 1994[9]	Of 19 Lyme arthritis patients treated with either parenteral antibiotics or long courses of oral antibiotics, PCR confirmed *Borrelia burgdorferi* detected in synovial fluid of 37% of patients.
Nocton et al. 1996[10]	Bb DNA was detected in CSF samples of 11 (25%) of 44 with chronic neuroborreliosis. Significant correlation between PCR results and the duration of previous intravenous antibiotic therapy.
Oksi 1999[11]	40% (13 of 32)) patients had clinical relapses that were PCR or culture-confirmed.
Pfister et al. 1991[12]	"In one patient *Borrelia burgdorferi* was isolated from the cerebrospinal fluid 7.5 months after ceftriaxone therapy.... [P]rolongation of therapy may be necessary."
Preac Mursic 1996[13]	*Borrelia burgdorferi* was isolated by culture in 5 patients, 4 of whom had previously tested antibody-negative.
Preac-Mursic 1993[14]	Patient with blurred vision treated with two separate month-long cycles of tetracycline had symptoms persist for several years. *Borrelia burgdorferi* cultures from iris biopsy.
Priem et al. 1998[15]	Although "PCR... was negative in synovial fluid and urine," PCR confirmed *Borrelia burgdorferi* in synovial membrane of 4 previously treated patients with Lyme arthritis.
Schmidli et al. 1998[16]	*Borrelia burgdorferi* was cultured from joint fluid after treatment.

Animal studies	
Straubinger et al. 1997[17]	30 days treatment "diminished but failed to eliminate persistent infection" in dogs. Antibody titers fell, but "after antibiotic treatment was discontinued antibody levels began to rise again, presumably in response to proliferation of the surviving pool of spirochetes."
Straubinger 2001[18]	All 8 infected dogs previously treated with 30 days antibiotics were PCR positive from tissue samples after necrosis. 25 tissue samples per dog were used.
Hodzik et al. 2008[19]	"[F]ollowing antibiotic treatment, mice remained infected with nondividing but infectious spirochetes."

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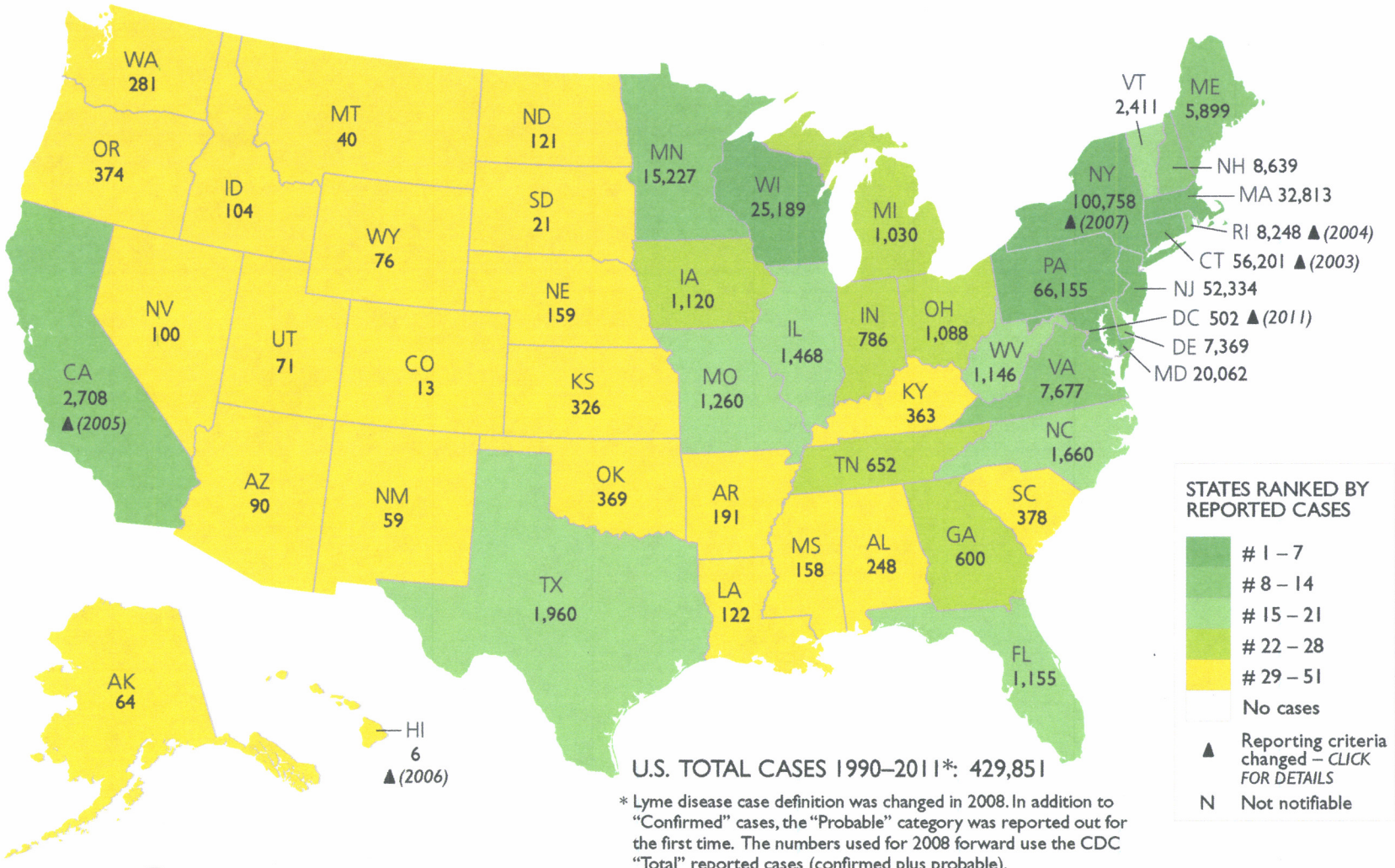
TOTAL LYME CASES REPORTED BY CDC 1990–2011*



U.S. TOTAL CASES 1990–2011*: 429,851

* Lyme disease case definition was changed in 2008. In addition to "Confirmed" cases, the "Probable" category was reported out for the first time. The numbers used for 2008 forward use the CDC "Total" reported cases (confirmed plus probable).

Note: According to CDC only 10% of Lyme disease cases that meet the case definition are reported, meaning if 10,000 cases are reported, 100,000 cases occurred. This data does not include all the cases that fall outside the stringent surveillance case definition.

Source: Data compiled from CDC pub. data (MMWR)

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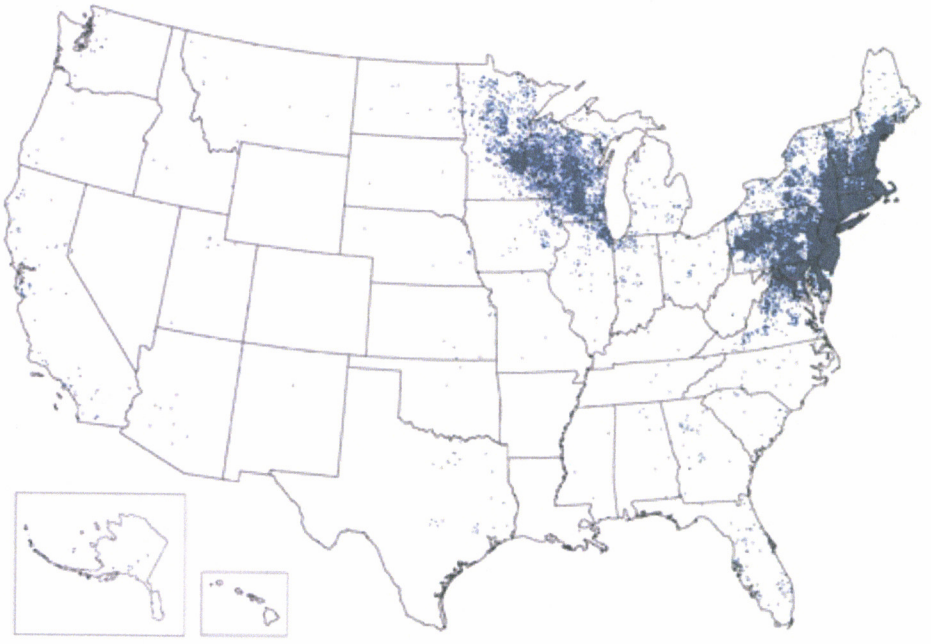
Reported Cases of Lyme Disease -- United States, 2001

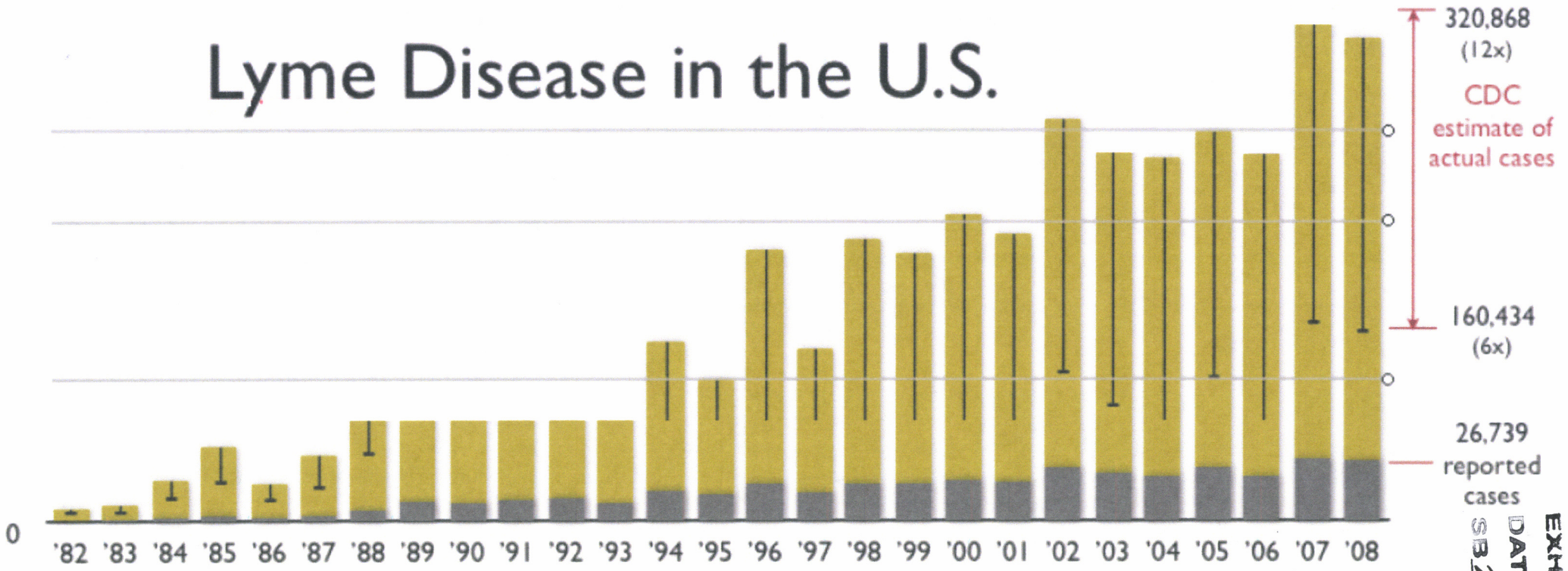
1 dot placed randomly within county of residence for each reported case

Reported Cases of Lyme Disease -- United States, 2011



1 dot placed randomly within county of residence for each confirmed case

Lyme Disease in the U.S.



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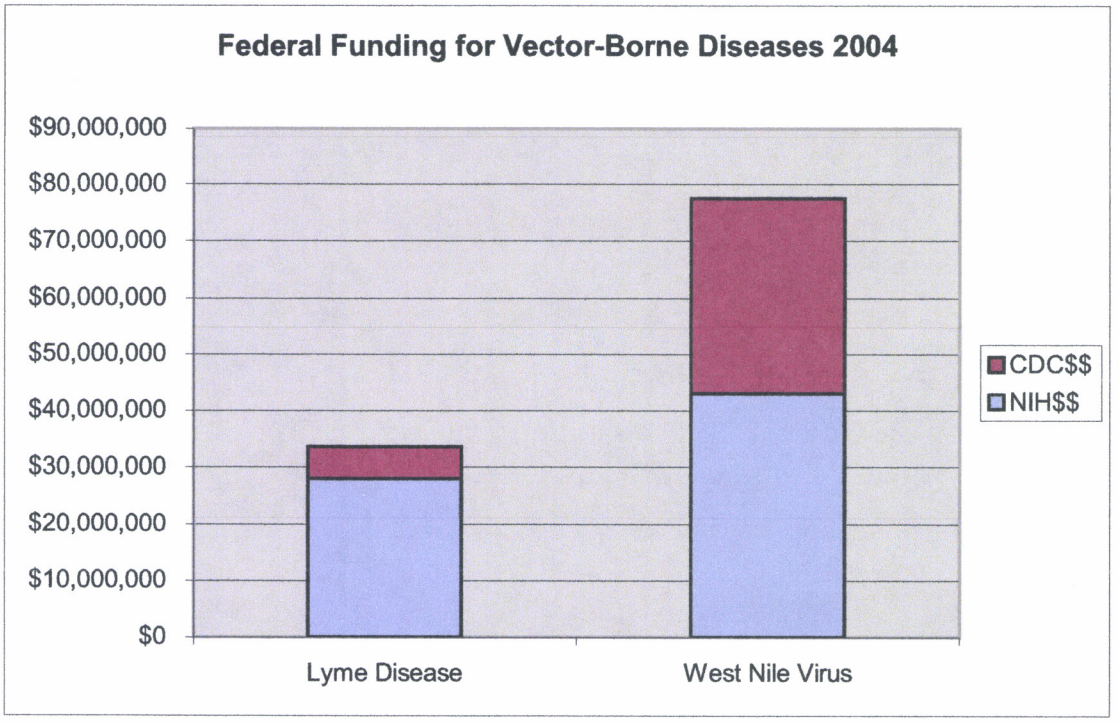
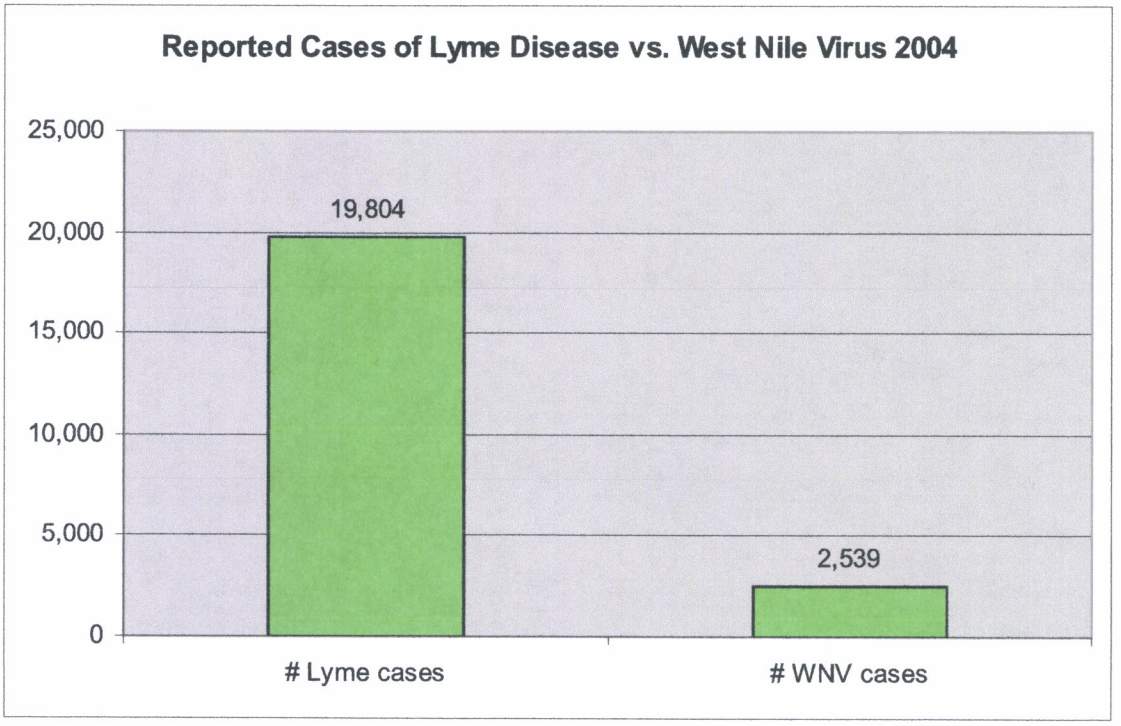
Disparity in Funding: Lyme vs. West Nile





Lyme disease is almost eight times more commonly reported than West Nile Virus in the U.S., yet the government spends **18 times** more money on each case of WNV.

California Lyme Disease Association 2004

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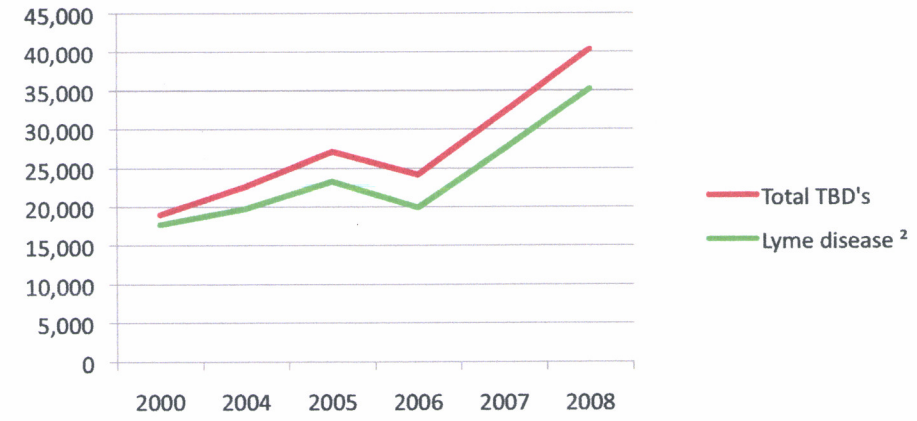
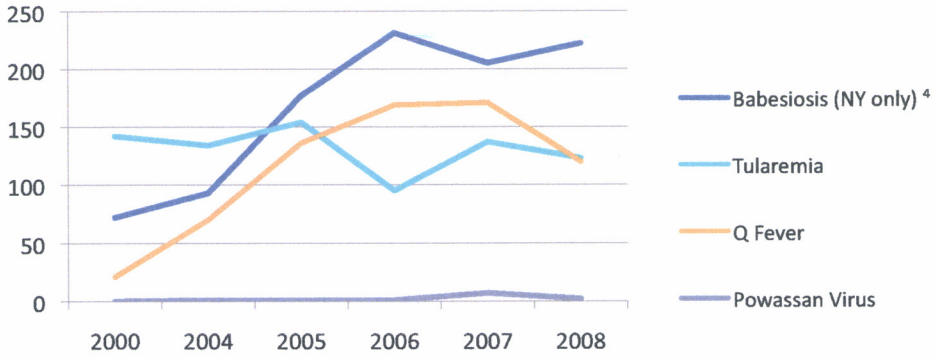
Lyme Disease Association Report
Tick-Borne Diseases Reportable Cases Analysis





(1) Source data compiled: CDC (MMWR) for all diseases except Babesiosis.

(2) Lyme disease case definition was changed for 2008 and the category of probable was reported for the first time. (2008 confirmed = 28,921 / probable = 6,277) The numbers used in 2008 include confirmed and probable cases reported by CDC. According to the CDC, only 10% of Lyme disease cases that meet the case definition are reported, meaning if 10,000 cases are reported, 100,000 cases occurred. This data does not include all the cases that fall outside the stringent surveillance case definition.

(3) RMSF (Rocky Mountain spotted fever) case definition changed for 2008 and the category of probable was reported for the first time. (2008 confirmed = 190 / probable = 2,367)

(4) Babesiosis is not a national notifiable disease. Figures were obtained from New York State Department of Health.

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Bacterial forms: characteristics and treatments			
	Spirochete	**Cell-Wall-Deficient (CWD)**	**Cyst**
Primary bacterial activities and characteristics that facilitate survival	Very mobile. Spiral/drill capable shape allows penetration into dense tissue and bone. Capable of intracellular infection. Rapidly converts to CWD and cyst form when threatened.	Lack of cell wall makes targeting by immune system and antibiotics more difficult. Capable of intracellular infection. Converts Vitamin D to immunosuppressive hormone known as 1,25-D. Causes autoimmunity. Clumps together in dense colonies—inner layers unreachable by antibiotics and immune system.	Dormant form bacteria are not mobile and do not cause symptoms. Can survive antibiotics, starvation, pH changes, hydrogen peroxide, temperature variation, and most other adverse conditions. Converts back to spirochete form when conditions are favorable.
Symptoms	Conventionally recognized Lyme Disease symptoms, i.e., bull's-eye rash, Bell's palsy, flu-like symptoms, fever.	Numerous syndromes and conditions not conventionally attributed to Lyme Disease, i.e., paralysis, multiple sclerosis, mental disorders, chronic fatigue syndrome, "post-Lyme syndrome," many more.	Does not cause symptoms
Common (yet not fully accurate) beliefs	Causative bacteria in Lyme Disease.	Not recognized or acknowledged; insignificant bacterial form.	Not recognized or acknowledged; insignificant bacterial form.
Correct beliefs	Causative bacteria in early-stage Lyme Disease, but not even close to the whole story.	Causative bacteria in many Lyme Disease symptoms and problems. As or more dangerous than spirochete form. Very difficult to treat.	Responsible for "relapsing and remitting" Lyme Disease. Can persist unrecognized and asymptomatic for many years.
Conventional treatment and success rates	Pharmaceutical antibiotics. Sometimes successful if infection is caught early. Often causes conversion to CWD and cyst form.	Often misdiagnosed as autoimmune or psychiatric disorders and mistreated with steroids, painkillers, antidepressants. Symptoms are often deemed idiopathic. Very low success rate.	Asymptomatic so conventionally not treated with anything. Frusteration and confusion experienced by patient and practitioner upon inevitable relapses due to cysts.
Proper treatment (as described in this book) and success rates	Rife machine therapy is the preferred treatment, and is the only known treatment that kills spirochetes and does not induce conversion to CWD and cyst form. Highly successful.	Marshall Protocol is preferred treatment and is typically successful, often leading to remission of "incurable" diseases, ranging from autoimmune diseases to mental disorders to chronic fatigue syndrome.	Cyst form antibiotics (5-nitroimidazoles) are somewhat successful. Avoidance of cell wall inhibiting antibiotics (e.g. Rocephin) and use of a rife machine (to kill spirochetes that emerge from cysts) is highly successful.

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